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# ACUTE KIDNEY INJURY AFTER CORONARY ARTERY BYPASS GRAFTING AND OUTCOMES

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# ACUTE KIDNEY INJURY AFTER CORONARY ARTERY BYPASS GRAFTING AND OUTCOMES

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Nanna Svartz Auditorium, Karolinska Universitetessjukhuset Solna

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**TO CHARLES & CHANELLE**

# ABSTRACT

Acute kidney injury (AKI) is a rapid reduction in glomerular filtration rate (GFR) that leads to a rise in serum creatinine (SCr). Acute kidney injury is common and patients with sepsis and patients who undergo cardiac surgery are at highest risk. Acute kidney injury is a potentially life-threatening complication that affects 9–40% of patients who undergo coronary artery bypass grafting (CABG). The associations between AKI and postoperative complications, long-term myocardial infarction (MI) risk, stroke and end-stage renal disease (ESRD) are not well described. The overall aims of this thesis are to study the associations between AKI after CABG and postoperative complications, short- and long-term mortality, long-term MI risk, stroke and ESRD.

Study I investigated the association between AKI after an initial isolated CABG and postoperative complications and death within 60 days of surgery. Of 7594 patients, 1047 (14%) patients developed AKI as defined by the Acute Kidney Injury Network (AKIN) classification. Patients with AKI had increased risk for death and postoperative complications. Multivariable adjusted odds ratios (OR) with 95% confidence intervals (CI) in patients in AKIN stage 1 compared with patients without AKI were 4.36 (95% CI: 2.83–6.71) for short-term mortality; 2.34 (1.43–3.82) for stroke; and 2.88 (1.84–4.50) for mediastinitis compared with patients without AKI.

Studies II-IV investigated associations between AKI and long-term risks for mortality, MI, stroke or ESRD in a nation-wide cohort of almost 30 000 patients who underwent first elective CABG, 13% of whom developed AKI postoperatively. Associations were seen between MI, mortality and AKI, with hazard ratios (HR) for MI and death increasing with AKI severity. Adjusted HR for patients with AKI stage 1 were 2.92 (95% CI: 1.87–4.55) for ESRD; 1.35 (95% CI: 1.15–1.57) for MI; and 1.30 (95% CI: 1.17–1.44) for all-cause mortality compared with patients without AKI. Although we found no association between AKI and long-term risk of stroke, a subgroup analysis showed an increased long-term risk for postoperative stroke among patients younger than 65 years.

In conclusion, AKI after CABG was associated with increased risks for postoperative death, stroke, and mediastinitis. AKI was also strongly associated with long-term mortality, MI and ESRD after CABG, but not with long-term risk of stroke.

***Key words**: Acute Kidney Injury, Coronary Artery Bypass Grafting, Stroke, End-stage Renal Disease, Mortality, Postoperative Complications.*

# LIST OF PUBLICATIONS

This thesis is based on the following papers, referred to by their Roman numerals as follows:

I. **Acute kidney injury following coronary artery bypass grafting: early mortality and postoperative complications**
Linda Rydén, Staffan Ahnve, Max Bell, Niklas Hammar, Torbjörn Ivert, Martin J. Holzmann
*Scandinavian Cardiovascular Journal 2012; 46: 114–20*

II. **Acute kidney injury after coronary artery bypass grafting and long-term risk of myocardial infarction and death**
Linda Rydén, Staffan Ahnve, Max Bell, Niklas Hammar, Torbjörn Ivert, Ulrik Sartipy, Martin J. Holzmann
*International Journal of Cardiology 2014; 172:190-5*

III. **Acute kidney injury and long-term risk of stroke after coronary artery bypass surgery**
Martin J. Holzmann, Linda Rydén, Ulrik Sartipy
*International Journal of Cardiology 2013; 168:5405-10*

IV. **Acute kidney injury after coronary artery bypass grafting and long-term risk of end-stage renal disease**
Linda Rydén, Ulrik Sartipy, Marie Evans, Martin J. Holzmann
*Circulation 2014; 130:2005-11*

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ACE | Angiotensin Converting Enzyme |
| AKI | Acute Kidney Injury |
| AKIN | Acute Kidney Injury Network |
| AUC | Area Under the Curve |
| ARF | Acute Renal Failure |
| CABG | Coronary Artery Bypass Grafting |
| CAD | Coronary Artery Disease |
| CHF | Congestive Heart Failure |
| CI | Confidence Interval |
| CI-AKI | Contrast Induced Acute Kidney Injury |
| CKD | Chronic Kidney Disease |
| CPB | Cardio Pulmonary Bypass |
| DM | Diabetes Mellitus |
| EF | Ejection Fraction |
| ESRD | End-stage Renal Disease |
| eGFR | Estimated Glomerular Filtration Rate |
| GFR | Glomerular Filtration Rate |
| HA-AKI | Hospital Acquired Acute Kidney Injury |
| HR | Hazard Ratio |
| ICD | International Classification of Disease |
| ICU | Intensive Care Unit |
| IL | Interleukin |
| KDa | Kilo Dalton |

| | |
|---|---|
| KDIGO | Kidney Disease: Improving Global Outcomes |
| KIM-1 | Kidney Injury Molecule-1 |
| LVF | Left Ventricular Function |
| MDRD | Modification of Diet in Renal Disease |
| MI | Myocardial Infarction |
| NGAL | Neutrophil Gelatinase-Associated Lipocalin |
| NPR | National Patient Register |
| OR | Odds Ratio |
| PCI | Percutaneous Coronary Intervention |
| PY | Person Years |
| RCT | Randomized Controlled Trial |
| RIFLE | Risk, Injury, Failure, Loss of Kidney Function, End-stage Renal Disease |
| ROC | Receiver Operating Characteristics |
| SCr | Serum Creatinine |
| SD | Standard Deviation |
| SWEDEHEART | Swedish Web-system for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies |

# INTRODUCTION

Acute kidney injury (AKI) is defined as an abrupt decrease in the kidneys´ ability to filter waste products, thus leading to increased blood levels of metabolites such as creatinine. The incidence of AKI is increasing worldwide.[1] Acute kidney injury affects patients in all clinical settings but is most prevalent among septic patients in the intensive care unit (ICU) and among patients after cardiovascular surgery.[1-3]

Over the last decade, even very small increases in serum creatinine (SCr) have been shown to be associated with adverse outcomes in hospitalized patients.[4, 5]

Coronary artery disease (CAD) is widespread, and is the main cause of death in Sweden.[6] Coronary artery bypass grafting (CABG) is an efficient treatment for patients with obstructive CAD and is associated with better survival among high-risk patients compared with medication or percutaneous coronary intervention (PCI).[7] Because of this, and in combination with improved surgical and anesthetic skills, older and more fragile patients have been undergoing CABG. This has led to an increasing number of postoperative complications.[8]

This thesis aims to elucidate the effects of AKI, including small changes of creatinine levels after CABG, and the risks for postoperative complications, short and long-term mortality, development of stroke, myocardial infarction (MI) and end-stage renal disease (ESRD).

# BACKGROUND

## DEFINITION OF ACUTE KIDNEY INJURY

Acute kidney injury is a rapid reduction in glomerular filtration rate (GFR) that leads to a rise in SCr.[1] It is a common complication in various clinical settings. About 1–5% of hospitalized general surgical and medical patients are affected by AKI.[9] Acute kidney injury is associated with adverse outcomes and high health care costs.[10, 11] The most common cause of AKI is sepsis, which affects up to 70% of septic ICU patients.[12, 13] However, patients who undergo cardiac surgery have also been shown to be at great risk for AKI.[10, 14]

The term "acute renal failure" (ARF) was used until 2004 for cases when a patient´s GFR suddenly decreased. However, ARF had no standard definition at that time. More than 35 different definitions of ARF were reported in the literature, ranging from a small increase in SCr to renal failure requiring dialysis.[10, 15, 16] In a systematic review of 28 studies of preoperative risk factors for postoperative ARF, 26 different definitions were used.[17] This made comparison of outcomes from different studies impossible. Patients with ARF after extensive surgery, especially those in need of dialysis, were known to have increased risk of postoperative mortality.[15, 18] From 2004 to 2006, several studies found associations between small changes in postoperative SCr levels and increased postoperative risk of death.[4, 5, 12]

### Risk, Injury, Failure, Loss of Kidney Function, End-stage Renal Disease classification

In 2004, the Acute Dialysis Quality Initiative introduced a new common classification of AKI called RIFLE (Table 1). This classification was based on acute elevations of SCr levels to various degrees or sudden decreases in estimated glomerular filtration rate (eGFR), compared with baseline levels of SCr or GFR, or a change in urine output over a specified time period. The term ARF was then replaced by the term AKI. RIFLE defines AKI by three different degrees of severity (R–Renal risk, I– Injury, F-Failure) and two outcomes (L– Loss of kidney function, E– End-stage renal disease).[19] The RIFLE classification has been validated in several studies for classification of AKI after CABG.[20, 21] Although the introduction of the

RIFLE criteria improved the definition of AKI and made measurement and comparison of outcomes after AKI much better, RIFLE had some limitations– for example, whether urine output criteria should be used or not; and whether changes in eGFR were a preferable metric than SCr. When urinary output criteria are used, the patient needs a urinary catheter, and urine output is often under the influence of diuretics. Estimated GFR is known to not be reliable in a situation without steady state.[22-24] Baseline SCr is missing in some studies, which makes classification impossible.[22] To handle missing baseline SCr values, some have suggested that they may be calculated backwards from the Modification of Diet in Renal Disease (MDRD) formula;[25] this might give very uncertain estimates.[26-28]

## Acute Kidney Injury Network classification

In 2007, the Acute Kidney Injury Network (AKIN) modified the RIFLE criteria. An absolute increase of 26.5 μmol/L (0.3 mg/dL) in SCr levels and a time interval of 48 hours when the increase should occur were added to the classification (Table 1). This classification was named the AKIN criteria.[29] In addition the eGFR criteria and the two outcome categories were abandoned. Finally, they allocated patients with AKI who required dialysis to stage 3 despite the severity of their AKI.[29] The AKIN criteria also recommend that AKI should only be diagnosed after adequate volume resuscitation, and that post-renal obstruction would need to be excluded if oliguria was present.

Acute kidney injury has also been classified in three groups by absolute numbers in some studies, for example, SCr rising from baseline by 0.3–0.5, 0.5–1.0 or >1.0 mg/dL.[5, 30, 31] This is based on the AKIN definition and is thought to be easier to use in clinical practice. Absolute creatinine changes may be more sensitive in detecting AKI at an early stage under certain circumstances.[32]

**Table 1**. **The RIFLE[19] and AKIN[29] criteria. Acute kidney injury should occur within 1 week for RIFLE and within 48 hours for AKIN.**

| Stage | Increase in serum creatinine from baseline | Urine output criteria |
|---|---|---|
| **RIFLE** | | |
| Risk | × 1.5 *or* GFR decrease >25% | <0.5 mL/kg/h for ≥6 h |
| Injury | × 2 *or* GFR decrease >50% | <0.5 mL/kg/h for ≥12 h |
| Failure | × 3 *or* GFR decrease >75% *or* baseline SCr ≥4 mg/dL (≥354 μmol/L) with an acute rise of ≥0.5 mg/dL (≥44.2 μmol/L) | <0.3 mL/kg/h for ≥24 h *or* anuria ≥12 h |
| Loss of Kidney Function | Complete loss of renal function >4 weeks | |
| End-stage Renal Disease | End-stage renal disease (>3 months) | |
| **AKIN** | | |
| Stage 1 | ≥0.3 mg/dL (≥26.5 μmol/L) *or* 150% to 200% (1.5- to 2-fold) | <0.5 mL/kg/h for ≥6 h |
| Stage 2 | >200% to 300% (>2- to 3-fold) | <0.5 mL/kg/h for ≥12 h |
| Stage 3 | >300% (>3-fold) *or* ≥0.5 mg/dL (≥44 μmol/L) if baseline SCr is ≥4.0 mg/dL (≥354 μmol/L). Patients on renal replacement therapy are considered in stage 3. | <0.3 mL/kg/h for ≥24 h *or* anuria ≥12 h |

RIFLE, Risk, Injury, Failure, Loss of kidney function, End-stage renal disease; AKIN, Acute Kidney Injury Network; AKI, acute kidney injury; SCr, serum creatinine; GFR, glomerular filtration rate.

## Kidney Disease: Improving Global Outcomes guidelines

Kidney Disease: Improving Global Outcomes (KDIGO) is an international group of experts who work to improve treatment for kidney diseases.[1] As KDIGO wanted a unified definition for AKI, they merged the AKIN and RIFLE criteria. Their definition for stage 1 AKI did not change in terms of absolute increases by SCr levels of 26.5 μmol/L (0.3 mg/dL) within 48 hours compared with AKIN. However, for the 50% increase in SCr levels from baseline, the defining time interval was changed to 7 days, as in RIFLE (Table 2).[33]

**Table 2**. **The Kidney Diseases: Improving Global Outcomes (KDIGO) guidelines for definition of acute kidney injury.[33] Increase in serum creatinine ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours or ≥1.5 times baseline, within the prior 7 days.**

| Stage | Serum Creatinine | Urine Output |
|---|---|---|
| 1 | 1.5–1.9 × baseline *or* ≥0.3 mg/dL (≥26.5 μmol/L) increase | <0.5 mL/kg/h for 6–12 h |
| 2 | 2.0–2.9 × baseline | <0.5 mL/kg/h for ≥12 h |
| 3 | 3 × baseline *or* increase in SCr to ≥4.0 mg/dL (≥354 μmol/L) *or* initiation of renal replacement therapy *or* in patients <18 years a decrease in eGFR to <35 mL/min/1.73 $m^2$ | <0.3 mL/kg/h for ≥24 h or anuria ≥12 h |

eGFR, estimated Glomerular Filtration Rate. SCr, serum creatinine.

The three main AKI classification systems have been compared in several articles. In studies of general ICU populations the RIFLE classification presented a higher incidence of AKI than did AKIN;[34, 35] however, the highest incidence occurred with the KDIGO classification.[35] Luo *et al*. showed higher mortality among patients in the AKIN group than in the KDIGO group (32% *vs*. 27%, $P = 0.006$),[35] whereas in AKI-related mortality did not significantly differ between RIFLE and KDIGO ($P = 0.815$).[35]

A Brazilian study of 169 patients who underwent CABG, showed a high incidence of AKI; 33% classified by AKIN and 30% by RIFLE. The mortality in the two groups was similar and the authors concluded that the AKIN and RIFLE classifications accord well in detecting AKI after CABG.[36] Bastin *et al*. classified 1881 adults undergoing cardiac surgery by AKIN, RIFLE and KDIGO criteria and found similar AKI incidences with AKIN and RIFLE; however receiver operator characteristic (ROC) analysis of in-hospital mortality favored AKIN (0.86 *vs.* 0.78, $P = 0.0009$). The incidence and outcome between AKIN and KDIGO were identical.[37]

## INCIDENCE AND OUTCOMES OF ACUTE KIDNEY INJURY

The incidence of AKI is increasing all over the world. Approximately 600,000 cases of AKI are reported in the United States every year and the incidence of AKI that require dialysis increases by >7% every year.[38, 39] This has several explanations. Consensus criteria like RIFLE and AKIN have improved diagnosis of AKI, the condition is more recognized, and several patient-related factors contribute to the increase, including an ageing population.[40] Increasing and extensive use of nephrotoxic drugs in diagnostic and treatment procedures could also explain this trend.[41]

In a meta-analysis of 312 studies concerning the world incidence of AKI, the authors found that among critically ill patients, one out of five adults and one out of three children developed AKI during hospitalization.[42]

The incidence of AKI varies in different settings. It is most common among ICU patients with sepsis, and after cardiac surgery. Li *et al*. found that in 64 patients who underwent elective CABG, 20% developed AKI (stage 1: 7.9%; stage 2: 3.5%; stage 3: 8.4%). It was highly prevalent in patients with diabetes mellitus (DM), 56%.[43] In a Swedish cohort of patients who underwent isolated CABG, early mortality was seen in 3.6% and long-term

mortality in 12% of isolated CABG patients.[44] Among patients with AKI after cardiac surgery, 11% died within 1 year and 56% within 10 years.[45]

## RISK FACTORS FOR ACUTE KIDNEY INJURY

Several factors are associated with the development of AKI. Sepsis is the most common cause, followed by cardiac surgery.[46-48] Critical illness, burns, trauma, and exposure to radio contrast material are other frequently described causes.[33, 40, 49] However, the individual patient´s susceptibility determines whether an exposure will lead to AKI. Dehydration, congestive heart failure, advanced age, chronic kidney disease (CKD), anemia and DM are examples of potential predisposing factors.[33] Although more than one third of AKI cases are reportedly community-acquired,[33] community-acquired AKI (CA-AKI) is not widely studied. In a worldwide meta-analysis of AKI, defined using a KDIGO equivalent, CA-AKI was compared with hospital acquired AKI (HA-AKI). The pooled CA-AKI incidence was 8.3% and the incidence rate of HA-AKI was 12–31%, depending on hospital setting.[42] Wonnacott *et al*. found opposite relations between community acquired and hospital acquired AKI. The incidence of HA-AKI was 2.1% and the incidence of CA-AKI was 4.3%, with an over-all incidence of 6.4%.[50] The patients with HA-AKI was marginally older than those with CA-AKI but despite that they carried the similar demographic and risk factors, but patients with CA-AKI had better short- and long-term outcomes.[50]

The most common causes of HA-AKI—sepsis, cardiac surgery and exposure to radio-contrast material—will be further described.

### Sepsis

Sepsis is the most common cause of AKI; 45–70% of all AKI is shown to be associated with sepsis.[13, 46] In the ICU, >50% of all cases of AKI are caused by sepsis.[51] Among patients in a multicenter study >64% of patients with septic shock developed AKI within 24 hours of ICU admission. Patients with delay in receiving antibiotics had higher risk of developing AKI, and patients with AKI had increased mortality risk in the ICU (Odds Ratio (OR): 1.73; 95% confidence interval (CI): 1.6–1.9) and hospital (OR: 1.62; 95% CI: 1.5-1.7).[52] Mehta *et al*. described an association between sepsis and AKI and also indicated that AKI predisposes for sepsis.[53]

Formerly, AKI in sepsis was thought to be caused by changes in renal circulation leading to renal ischemia, cellular damage and acute tubular necrosis.[54] Now, several studies suggest that AKI can develop in the absence of hypoperfusion, and might be caused by alterations in intra-renal circulation leading to endothelial dysfunction, inflammation, and coagulopathy.[55-59] Murugan *et al.* showed that most patients with sepsis are not admitted to the ICU, and do not express hemodynamic instability, despite this is AKI common.[60]

## Cardiac surgery

In 1998 Chertow *et al.* showed that ARF was independently associated with early mortality following cardiac surgery.[11] As CABG has become a generally accepted and safe treatment for CAD, patients who undergo CABG have become older and affected by more co-morbidities.[8] As patients with less severe CAD are increasingly treated with PCI, the percentage of CABG-treated patients who have advanced CAD has also increased.[8]

Cardiac surgery is the second most common cause of AKI; the incidence of cardiac surgery-associated AKI is 8.9–39%[61, 62] In cardiac surgery CABG is the procedure associate with the lowest risk for AKI, whereas combined procedures such as valvular replacement and concurrent CABG are associated with highest risk.[45] Some risk factors for AKI are patient related, female sex, and comorbidities such as chronic obstructive pulmonary disease, diabetes mellitus (DM), low ejection fraction (EF), congestive heart failure, peripheral vascular disease, and CKD. Some other factors are procedure-related such as length of cardiopulmonary bypass (CPB),[61, 63] use of an intra-aortic balloon pump, on pump more than off-pump surgery, non-pulsatile flow, decreased renal perfusion, hemolysis with release of free iron, inflammation, oxygen free radicals, oxidative stress and hemodilution.[64, 65] The need for emergent surgery is also an important predictor for AKI.[64]

Moreover, patients who undergo CABG, may have increased risk for AKI due to contrast exposure during coronary angiographies that has been performed just before surgery.

## Contrast-induced acute kidney injury

Contrast-induced AKI (CI-AKI) after coronary angiography is the third leading cause of AKI among hospitalized patients,[9, 66] with reported incidence of 2.6–13%.[67, 68] An eGFR of less than 60 mL/min/1.73m$^2$ is the most important risk marker for CI-AKI.[69] Patients with

hypotension, intra-aortic balloon pumps, heart failure, DM, and age older than 75 years are also at high risk.[70] A consensus group stated that the risk for CI-AKI is clinically important when baseline SCr is >1.3 mg/dL (>115 μmol/L) for men and >1.0 mg/dL (88.4 μmol/L) for woman, which corresponds to an eGFR <60mL/min/1.73m$^2$.[69] Another study found that the incidence of AKI only became significant when iodinated contrast material was given to patients with a baseline SCr >1.8 mg/dL (>159 μmol/L).[71]

In AKI after coronary angiography, even small increases of SCr are associated with adverse outcomes but the mechanism is under debate. James *et al*. wrote a thorough review on the subject in which they concluded that CI-AKI is associated with increased risk of mortality, cardiovascular events and prolonged hospitalization, but the association is strongly confounded by several baseline characteristics of patients which are predictors for increased risks of both mortality and AKI.[66] The risk for death after CI-AKI is overestimated in several studies, because adjustments for confounders were not performed.[66]

In a recent study on >20 000 patients undergoing abdominal, thoracic or pelvic computer tomography the authors showed no difference in AKI-incidence, dialysis or 30-day mortality between patients receiving intravenous low-osmolar or iso-osmolar contrast material compared to those not receiving any contrast material.[72]

## PATHOPHYSIOLOGY OF ACUTE KIDNEY INJURY

The pathophysiology of AKI is a complex, multifactorial process with several different mechanisms. Historically, it has been divided into three categories: (1) The prerenal cause of AKI is reversible reduction of glomerular filtration rate due to decreased renal perfusion; for example due to hypovolemia, decreased cardiac output or severe vasoconstriction.[73] (2) Renal causes of AKI include classical kidney diseases such as glomerulonephritis and nephrotoxic drugs such as contrast material, some antibiotics, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs) and angiotensin converting enzyme (ACE) inhibitors.[74, 75] Although studies on the use of ACE inhibitors before cardiac surgery present both reduction in AKI[76] and is associated with increased AKI risk,[77] whether ACE inhibitors cause AKI or exacerbate AKI by vasodilatation of efferent arterioles leading to decreased GFR is unclear.[78] (3) Postrenal causes of AKI include conditions that cause mechanical obstruction of urinary flow, such as benign prostate hypertrophy, tumors and kidney stones. If these obstructions persist, permanent damage may ensue.

A contemporary way of classifying AKI mechanism considers vascular, tubular, and inflammatory pathways, which are the same if the injury is caused by ischemia/reperfusion, toxins or sepsis.[79] An injury that starts with trauma, for example, may cause a reduction in perfusion. This leads to depleted cellular adenosine triphosphate (ATP) and oxidative stress with release of cytokines and chemokines that recruit inflammatory cells. The inflammatory cells release more cytokines that worsen the epithelial injury. This causes loss of proximal tubular cytoskeletal polarity and integrity, which leads to a mislocalization of important membrane proteins such as Na/K-ATPases, detachment of tubular brush border cells from the basement membrane, apoptosis and necrosis.[80] If the injury is severe enough, cellular debris is shredded out in the tubular lumen and parts of the basement membrane are left exposed as the sole barrier between the filtrate and the peritubular interstitium. These naked areas, combined with increased pressure in the tubules (due to cellular debris causing obstruction) can cause back leak of fluid and interstitial edema.[79] Instantly, in response to the injury, viable epithelial cells start the repair process. In a favorable milieu with nutrients and oxygen, migration and division of epithelial cells (re-differentiation) restores and heal the brush border, and cellular polarity and integrity recover.[81] However, in prolonged ischemia, the inflammatory response exacerbates the injury due to release of inflammatory mediators and vasoconstrictors.[79] Whether other pathways of tubular injury exist—for example severe ischemia that leads to transformation of epithelial cells into fibroblasts, thus promoting fibrosis and chronic kidney disease—is a point of debate. Other studies suggest that the kidney heals with development of fibrosis, which could explain why AKI seems to accelerate progression of CKD.[79, 82]

## PATHOPHYSIOLOGY OF CARDIAC SURGERY ASSOCIATED ACUTE KIDNEY INJURY

In a review article by Bellomo *et al.* the pathophysiology of cardiac surgery associated AKI is explained in six different mechanisms and/or pathways; Exogenous and endogenous toxins, metabolic factors, ischemia-reperfusion, neurohormonal activation, inflammation and oxidative stress.[65] The authors point out that causation cannot be established, and to perform a RCT to evaluate the effect of a single factor is difficult since the different pathways and factors act synergistically.

Exogenous toxins, for example some antibiotics, contrast material, ACE inhibitors and NSAIDs could harm the kidneys in some patients. Hemolysis during CPB causes release of

free hemoglobin and iron, which can act as endogenous toxins. Also rhabdomyolysis can occur, which in turn can act as an endogenous toxin.[65]

Metabolic factors including DM are independently associated with AKI and DM is common among patients having CABG.[65, 83, 84] Extremes of body mass index are also associated with AKI.[65]

Ischemia can be caused by a variety of disorders; hemodynamic instability with low cardiac output, hypovolemia, overdose of vasodilator, or renal artery embolism originated from for example the time of cardiac catheterization and cannulation. Air embolism can also cause ischemia.[65]

During anesthesia and CPB mean arterial pressure is often in the lower range of the kidneys autoregulatory limit of 80 mmHg.[83] Long duration of CPB, low flow and longer periods with mean arterial pressure less than 60 mmHg have been associated with AKI.[85] When CPB is discontinued the remaining heparin in the circulation is reversed with protamine that causes vasodilatation and hypotension leading to a low cardiac output. A low intravascular volume may also lead to impaired renal perfusion.[65] A balanced use of vasopressors and volume infusion is vital for the kidney perfusion.

There are several neurohormonal responses to CPB that are affected by cross-clamp time and duration of CPB. For example plasma levels of norepinephrine, epinephrine, vasopressin and dopamine are elevated during CPB. This leads to a reduction in renal blood flow and a reduction of GFR.[65] Use of CPB is associated with a systemic inflammatory response during and after cardiac surgery.[86] Some studies have used sodium bicarbonate in a nephro preventive action for oxidative stress postoperatively, however without effect.[65, 87]

## PREVENTION AND TREATMENT OF ACUTE KIDNEY INJURY

Maintaining balanced volume status is important in preventing and treating AKI. The goal is to keep a mean arterial pressure and to restore cardiac output to reach an adequate renal perfusion pressure and oxygen delivery. Hypovolemia is known to be a risk factor for AKI. However, some studies have associated fluid overload with adverse outcomes such as increased 60-day mortality, prolonged ventilator use among patients with acute lung injury, and worse cardiac function after cardiac surgery.[88-91] In a review article, Prowle *et al*. concluded that critically ill patients with AKI are at a high risk of fluid overload, which can

cause high central venous pressure and congestion in the kidney and lead to decreased GFR. Fluid overload is associated with adverse outcomes and can contribute to persistent AKI.[92] Prowle *et al*. suggest a thorough assessment of fluid status during volume resuscitation.[92] The KDIGO work group suggest isotonic crystalloids at initial management for volume optimization in patients at risk for, or with established AKI.[33] The use of vasopressors combined with fluids is also recommended.[33]

Several studies have investigated the effect of inflammation induced by CPB.[93, 94] Hypothetically, remote ischemic preconditioning can mitigate inflammation, but study results vary. Some studies show remote ischemic preconditioning to have no effect during cardiac surgery.[94-96] A randomized controlled trial (RCT) that investigated remote ischemic preconditioning in patients who underwent CABG showed the incidence of AKI to be reduced by 48%.[97] A smaller RCT showed reduced risk of AKI among patients who underwent ischemic preconditioning.[98]

Sodium bicarbonate reportedly reduces the incidence AKI after cardiac surgery, but a systematic review by Tie *et al*. found no benefits in using sodium bicarbonate to prevent AKI.[99] Instead, it prolonged mechanical ventilation and ICU stays, and increased risk for alkalemia.[99] Haase *et al*. showed no reduction in incidence of AKI and increased mortality among patients who underwent cardiac surgery and received sodium bicarbonate; this study was stopped early because of lack of efficacy and possible harm.[87]

## RENAL FUNCTION

### Kidney physiology

Kidneys play important roles in several vital anatomical systems. Every minute, 20% of the cardiac output passes through the kidneys.[73] The main function of the kidneys is to clean the blood of water-soluble waste products from our metabolism and excretion of some foreign toxins and medications. Through production of urine, kidneys regulate the balance of fluids and electrolytes within the body, acid-base balance, and blood pressure. Kidneys also produce several important hormones such as erythropoietin, which is vital for production of red blood cells and vitamin D.[73] The kidney has a special blood supply to the renal medulla; the medulla functions well at low oxygen tension, but, is very sensitive to changes in blood flow.

## Glomerular filtration rate

The definition of GFR is volume of plasma filtered by the kidneys per minute.[73] The normal GFR range is 90–130 mL/min/1.73m$^2$.[100] Starting around the fifth decade of life, GFR decreases by about 10 mL/min/1.73m$^2$ each decade.

GFR can be determined by using an exogenous substance that is freely filtered by the kidneys. Inulin clearance is considered gold standard for measurement of kidney function but this method is complicated, time-consuming and expensive.[101]

Serum creatinine is affected by several factors, such as muscle mass, liver disease, inflammation and muscle wasting, which limit the accuracy of creatinine testing.[102] To overcome these limitations, several formulas have been developed to increase the precision of estimates by incorporating age, ethnicity, sex, body size and serum creatinine concentration as variables. Most GFR estimation formulas work quite well in patients with GFR < 60 but are less precise in patients with high GFRs.

### *Formulas for estimation of glomerular filtration rate*

Three main formulas are used to estimate GFR. The Cockcroft–Gault formula was developed in 1973. This formula does not take body size into account and tends to overestimate GFR in obese patients and underestimate GFR in elderly patients.[103] The Cockcroft–Gault formula has been validated in several studies and is considered to be accurate for patients younger than 65 years with eGFRs between 20–60 mL/min/1.73m$^2$.

The Modification of Diet in Renal Disease (MDRD) Study Equation was developed in 1999. It has been simplified to four variables (age, ethnicity, sex, serum creatinine).[25] MDRD is more precise than the Cockcroft–Gault formula but it underestimates GFR among patients with GFR >60 mL/min/1.73m$^2$.

The Chronic Kidney Disease-Epidemiology Collaboration formula was developed in 2009. It uses the same parameters as the MDRD formula. It functions as well as MDRD among individuals with GFR <60 mL/min/1.73m$^2$, but is more precise among those with GFR >60 mL/min/1.73m$^2$.[104]

## CHRONIC KIDNEY DISEASE

Chronic kidney disease is a general term for a variety of conditions that affect the kidney. In 2002, the National Kidney Foundation´s Kidney Disease Outcome Quality Initiative presented guidelines for classification and evaluation of CKD.[23] The definition of CKD is based on the presence of kidney damage (albuminuria) or decreased kidney function (GFR <60 mL/min/1.73m$^2$) that persists for over 3 months. CKD is divided into five stages, depending on GFR value (Table 3).[23]

**Table 3. Stages of chronic kidney disease**

| Stage | GFR | Description |
|---|---|---|
| 1 | ≥90 | Kidney damage (albuminuria) with normal GFR |
| 2 | 60–89 | Kidney damage (albuminuria) with mild decrease of GFR |
| 3 a | 45–59 | Moderate reduction of GFR. In the US this is merged to one group with GFR 30–59. In Europe it is divided into two subgroups; 3a and 3b. |
| 3 b | 30–45 | |
| 4 | 15–29 | Severe reduction of GFR |
| 5 | <15 | Kidney failure. |

GFR, Glomerular filtration rate, mL/min/1.73m$^2$.

Several epidemiological studies have shown that patients with CKD are at a higher risk for death, development of cardiovascular disease, congestive heart failure and symptomatic peripheral vascular disease.[105-108] Severity of albuminuria and adverse outcomes like mortality in different populations have been related, even after adjustment for confounders such as low GFR and other risk factors for cardiovascular disease.[109, 110]

## SERUM MARKERS OF RENAL FUNCTION

### *Creatinine*

Creatine is synthesized in the liver from methionine, glycine and arginine but a small amount is also ingested through our diet, mainly meat. In skeletal muscle creatine is phosphorylated to form phosphorylcreatine, which is an important energy store for ATP synthesis. Muscle contains 98% of the total amount of creatinine in the body.[100] Creatinine is a 113 Da amino

acid product from the breakdown of phosphorylcreatine in muscle. Creatinine is distributed throughout the total body water and is freely excreted by the kidneys, primarily by glomerular filtration.[100] An estimated 10–40% of creatinine clearance is also actively secreted by tubular cells in the kidney and by extra renal secretion.[111] Because of this, creatinine clearance normally exceeds GFR.[102]

### *Cystatin C*

Cystatin C is a 13 kDa basic protein that is produced at a constant rate by all nucleated cells. Cystatin C is freely filtered by the glomerulus and metabolized by the tubular epithelial cells.[112] As no tubular secretion and only minimal extra-renal excretion occur, serum concentration of Cystatin C depends mainly on GFR.[113] Generation of Cystatin C seems to be less affected by age, sex and muscle mass than that of creatinine. However, corticosteroid use, high levels of C-reactive protein and hypo/hyperthyroidism affect the level of Cystatin C.[114, 115]

## BIOMARKERS FOR KIDNEY INJURY

The AKI definition is based on changes in levels of SCr, which is a surrogate marker for kidney injury. As SCr levels take several hours to begin to increase, and as much as 48 hours to peak after an injury to the kidney has occurred, an injury may be detected too late to prevent the injury from becoming permanent. A more sensitive biomarker that could detect kidney injury at an earlier stage would allow preventive actions to be taken. An ideal biomarker would be precise, reliable and highly sensitive for early-stage AKI. In addition, it would indicate the etiology of AKI (caused by, for example, sepsis, nephrotoxins, cardiac surgery, or contrast material). Ideally, it would also be inexpensive, easy to use and possible to standardize for clinical use,[116] and would indicate severity, and help monitor recovery, of AKI. Of several biomarkers at experimental stages, none fulfill all these criteria; however, a combination of different biomarkers might aid clinicians in diagnosing AKI in the future.

### *Kidney injury molecule -1*

Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein that is normally expressed in kidney tissue in small amounts. KIM-1 seems to be produced by proximal tubular cells in cases of kidney ischemia or if the kidney is affected by nephrotoxins.[117] KIM-1 transforms tubular epithelial cells into phagocytes that clear the lumen of cellular debris thereby aiding the process of regeneration and healing, and limiting the autoimmune response to apoptosis.[117-119] KIM-1 levels can be detected in urine, and increase when tubuli are injured. KIM-1 has been shown to be a sensitive biomarker for AKI after cardiac surgery[120] and is independently associated with long-term mortality.[121] In a recent investigation of the predictive abilities of 32 different biomarkers, alone or in combination, Arthur *et al*. found KIM-1 to be a good predictor for higher AKIN stage or death (area under the curve (AUC) 0.73), or for AKIN stage 3 or death (AUC: 0.81), but had a relatively weak correlation with the other markers studied.[122]

### *Neutrophil gelatinase-associated lipocalin*

Human neutrophil gelatinase-assocated lipocalin (NGAL) is a 25 kDa protein that is bound to gelatinase from neutrophils. NGAL is normally expressed at very low levels in kidneys, but its production in tubular cells increases markedly after renal injury.[123] Wagener *et al.* found urinary NGAL to rise significantly in the early postoperative period among patients who developed AKI after cardiac surgery.[124] In another study NGAL predicted progression of kidney injury or death after cardiac surgery relatively well (AUC: 0.72).[122]

### *Interleukin-18*

Interleukin 18 (IL-18) is an 18 kDa cytokine secreted by proximal tubular cells and leucocytes when tubular cells are injured.[125] In an animal model, inhibition of IL-18 protected against ischemic kidney injury, which support its significance in development of AKI.[125] Parikh *et al.* showed that IL-18 levels peak within 6 hours of cardiac surgery and were associated with development of AKI in the postoperative period.[126] In the aforementioned study of patients who underwent cardiac surgery, Arthur *et al*. showed IL-18 to be the best single predictor of the outcomes under study of the 32 tested biomarkers, and to have the highest predictive ability when combined with KIM-1.[122]

## FUROSEMIDE STRESS TEST

An established means of assessing kidney function among patients with oliguria is the use of furosemide. In a study of Baek *et al*. in 1973,[127] patients were each given a bolus of furosemide and free water clearance was evaluated. The authors concluded that acute renal failure was forthcoming in patients who did not respond to the furosemide bolus.[127] Even though this "furosemide test" is commonly performed at hospitals worldwide, it has no protocol or standardized execution, and had not been validated. In 2013, Chawla and colleagues showed that a single dose of 1.0 or 1.5 mg/kg of furosemide predicted if patients with early AKI would progress to AKIN stage III (AUC: 0.82–0.87),[128] which implies that, as a predictor of AKI, the furosemide stress test is as good or better than use of newer marker such as IL-18.[122] The furosemide stress test is also inexpensive, easy to perform and readily available.

## CORONARY ARTERY BYPASS GRAFTING

Coronary artery bypass and cardiac surgery are suitable for studying AKI, for two reasons. First, AKI is common after CABG, affecting 10−20% of patients in different cohorts; second, and most importantly, the timing of the injury is known, which is not true for patients with sepsis, for example.

The first successful open heart operation using CPB to close an atrial septal defect was performed in May 1953 by John Gibbon in Boston.[129] The second successful open heart operation in the world was done by Clarence Crafoord who removed an atrial myxoma in July 1954 at the Sabbatsberg Hospital in Stockholm.[130] Subsequent improvements in cardio-pulmonary bypass, surgical techniques, anesthesia and perioperative management opened up possibilities to perform extensive cardiac surgery. The first successful human CABG was performed in the United States 1960 by Dr. Goetz and Dr. Rothman.[131] Clinical introduction of CABG started after pioneering work at the Cleveland Clinics in 1967.[132] CABG evolved over the following decades to become a common surgical procedure. In 2012, 6009 open-heart procedures were performed in Sweden, of which 2736 were CABG (46%). In comparison, approximately 6500 CABG operations were done yearly in Sweden during the

90s. The number of cardiac surgeries performed worldwide has decreased during the last decade after the advent of PCI.[133]

Over the last decade, patients undergoing CABG have become older, with more comorbidities.[8] Patients with less severe CAD are more likely to be suitable for PCI, leaving patients with a more advanced CAD to surgery.[134] Several studies have shown that patients with two or more diseased coronary arteries have better long-term survival and a smaller risk of revascularization de novo when having CABG compared with PCI, including the use of drug-eluting stents.[134-139] Another study showed lower mortality rates in the CABG group than the PCI group.[136] In the FREEDOM (Future Revascularization Evaluation in patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial death or MI occurred more often after PCI than CABG in diabetic patients followed for five years.[140]

For prediction of perioperative mortality The European System for Cardiac Operative Risk Evaluation Score (EuroSCORE) was developed as a risk-scoring system for patients undergoing CABG.[141] It provides a simple additive risk model that consists of 18 variables divided into three groups; patient related, cardiac related and operation-related factors with different scores ranging from 1–4. The EuroSCORE 0-2 is considered low risk, 3-5 medium risk, and >6 high risk.[141] EuroSCORE is validated in several studies.[7, 142-144]

# AIMS OF THE THESIS

The overall aim of this thesis was to investigate the effect of AKI on short- and long-term outcomes after CABG. Our specific aims were:

- To study the association between AKI and short-term mortality and postoperative complications in patients who underwent CABG.

- To study the association between AKI and long-term mortality and risk for myocardial infarction and death in patients who underwent CABG.

- To study the association between AKI and the risk of stroke in patients who underwent CABG.

- To study the association between AKI and long-term risk of development of end-stage renal disease in patients who underwent CABG.

# SUBJECTS AND METHODS

Table 4 present an overview of study design and outcome measures in the thesis.

**Table 4. Summary of subjects and methods in the thesis.**

| | Study I | Study II | Study III | Study IV |
|---|---|---|---|---|
| Design | Single center, Cohort study | Nationwide Cohort study | Nationwide Cohort study | Nationwide Cohort study |
| Study population | Patients who underwent a first isolated CABG at Karolinska University Hospital | Patients who underwent a first isolated CABG in Sweden from SWEDEHEART | Patients who underwent a first isolated CABG in Sweden from SWEDEHEART | Patients who underwent a first isolated CABG in Sweden from SWEDEHEART |
| Number of subjects | 7594 | 27 929 | 23 584 | 29 330 |
| Study period | February 1995 to December 2006 | January 2000 to December 2008 | January 2000 to December 2008 | January 2000 to December 2008 |
| Statistical analysis | Logistic regression analysis. Receiver operator analysis | Multivariable hazard regression analysis | Multivariable hazard regression analysis | Multivariable hazard regression analysis |
| Outcome | Short-term mortality and postoperative complications | Myocardial infarction and long-term mortality | Long-term risk for stroke | ESRD and long-term mortality |

CABG, Coronary Artery Bypass Grafting; ESRD, End-stage renal disease; SWEDEHEART, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies.

## REGISTERS

### SWEDEHEART

The Swedish Web-System for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) is a national Swedish register with the aim of supporting evidence-based development of therapies in acute and chronic coronary artery disease and in catheter-based or surgical valve intervention. Additionally, the SWEDEHEART register aims to improve care for patients with coronary artery disease by making it possible for coronary care units to compare results

between each other, and to provide a basis for research.[145] National, regional and county-based reports are presented every year.[133] All clinics that treat patients with coronary artery disease report to SWEDEHEART on a yearly basis. The register consists of five parts; RIKS-HIA, the register on myocardial infarction care; SEPHIA, the register for secondary prevention following coronary intensive care; SCAAR, the register for coronary angiography and PCI; the Percutaneous Valve register; and The Swedish Heart Surgery Register. Baseline patient characteristics are collected at admission to hospital.

The Swedish Heart Surgery Register, where all adult heart surgery performed in Sweden is reported, was started in 1992. Heart surgery is currently performed at eight hospitals in Sweden.

The validation process of data in SWEDEHEART includes a visit by a monitor in approximately 20 random hospitals every year and compares information from medical records of 30–40 randomly chosen patients to the information in the register. Agreement between the information in the register and medical records is about 93–97%.[146] The validity of the information on postoperative complications is less reliable, as it depends on the thoroughness of the physician who does the registration.[133] The coverage of SWEDEHEART is 100% for patients undergoing cardiac surgery, angiography and PCI, and almost 100% for patients with acute coronary syndrome admitted to a coronary care unit—about 60% of all acute coronary syndrome cases.[146]

### The Swedish National Patient Register

The Swedish National Board of Health and Welfare started the National Patient Register (NPR) in 1964. Since 1987, it has covered the whole country.[147] The National Patient Register contains information on each patient's personal identity number, age, sex, place of residence, county, hospital/clinic, department, dates of admission and discharge, lengths of hospital stays, acute/planned admissions, admitted-from and discharged-to data, primary diagnoses, secondary diagnoses, external causes of injury or poisoning and procedures. All county councils in Sweden report this information yearly.[147] Discharge codes are classified according to the *International Classifications of Diseases* (ICD). Some variables are missing in NPR; in 2006, 0.6% of records were missing personal identity numbers and 1% were missing principal diagnoses.[147] In the NPR, MI[148] and stroke[149] as principal cause of hospitalization has a positive predictive value of 98%.

### The Cause Of Death Register

The Cause of Death Register was started in 1952 and is under the supervision of the Swedish National Board of Health and Welfare.[150] The Swedish Cause of Death Register contains all deceased people in Sweden since 1961. Information on date of death and contributing causes are also registered. About 1–2% of their records have a missing cause of death. The missing cases are coded without known cause of death.[150]

### The Swedish Renal Registry

The Swedish Renal Registry was founded in 2007 when several local registries in Sweden; the Swedish Register for Active Treatment of Uremia (1991) and the Swedish Dialysis Database merged to form a nationwide register.[151] All nephrology and transplantation units in Sweden report to this register through a webpage. It functions as a quality register for patients with ESRD under the supervision of the Swedish Society of Nephrology and the Swedish Transplantation Society.[151] Patients enter this register when they start their first active treatment for ESRD, or receive kidney transplants. Discontinuation of treatment leads to removal from the register.

### Total Population Register

The total population register is a part of Statistics Sweden. It includes such data as name, place of birth and residence, sex, age, civil status, citizenship, immigration and relationships such as married couples and child–parent.[6] The total population register is updated continuously. An estimated 93% of all death are reported to Statistics Sweden within 10 days and 100% within one month.[6]

### The Swedish Personal Identification Number

Since 1947, all citizens in Sweden carry a unique personal identity number. It consists of ten digits: the year and date of birth and a four-digit control number.[152] This personal identity number covers virtually the whole Swedish healthcare system and facilitates linkage between different registers in epidemiological studies.[152] When an individual stays in Sweden on a permanent basis and is recorded in the Total population register, they are given a personal identity number.

## STUDY POPULATION AND DATA COLLECTION

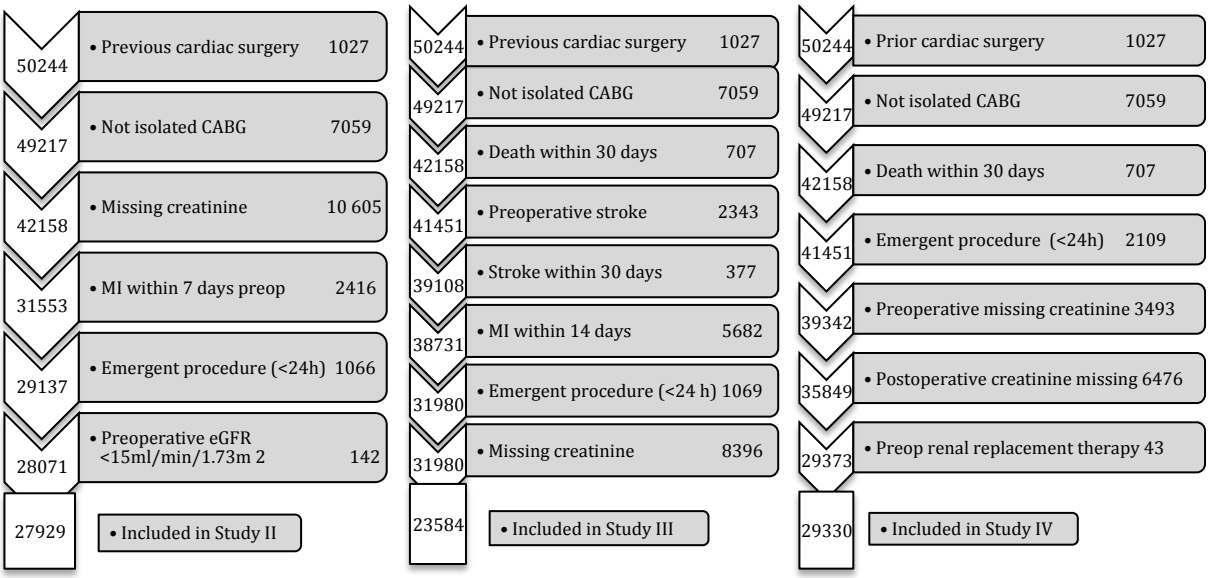
### Study I

This cohort was retrieved from a local database at Karolinska Hospital, and consisted of all 8298 patients who underwent a first isolated CABG between February 1995 and December 2006, excluding 704 patients because of missing information on pre-and/or postoperative SCr, leaving 7594 patients for final analysis. Several variables were collected prospectively from medical records: age, sex, weight, height, DM, peripheral vascular disease, left ventricular function (LVF), prior stroke or MI, acute coronary syndrome, pre- and postoperative SCr, dialysis dependent renal failure number of significantly obstructed coronary arteries, and date of surgery.

### Studies II-IV

The Studies II-IV cohorts were retrieved from the SWEDEHEART register and consisted of 50 244 patients who underwent CABG between 2000 and 2008 in Sweden. Exclusion criteria in study II–IV are presented in Figure 1.

**Figure 1**. **Exclusion criteria in study II, III, and IV.**



Information on the following clinical characteristics were collected from SWEDEHEART: age, sex, current smoking, preoperative eGFR, preoperative SCr, DM, hypertension, hyperlipidemia, peripheral vascular disease, chronic obstructive pulmonary disease, LVF, EuroSCORE, use of internal thoracic artery, off-pump surgery, and length of hospital stay.

Information on prior hospitalization for chronic obstructive pulmonary disease, congestive heart failure, prior MI, and prior stroke was obtained from the NPR. Information on prior renal replacement therapy was collected from SWEDEHEART.

## Laboratory method and other variables

### *Serum creatinine*

In all studies, GFR was estimated using the abbreviated MDRD formula[25] as follows;

$$eGFR = 186.3 \times (\text{SCr in } \mu\text{mol per L} / 88.4)^{-1.154} \times age^{-0.203} (\times 0.742 \text{ if female})$$

### *Study I*

Baseline SCr was measured at the time of admission to the ward, normally the day before surgery or within one week prior to surgery. Among 483 patients with AKI, we scrutinized all SCr values through medical records, during the entire hospitalization, and found that in 93% of patients the 48-hour SCr value corresponded to the highest postoperative value.

All serum creatinine samples were analyzed at the same laboratory at the Karolinska University Hospital Stockholm, Sweden. There was a change of analysis method in March 2005 from the nonkinetic alkaline Jaffé method to an enzymatic method with somewhat lower results. The results from the enzymatic method were corrected to correspond to the Jaffé method.

### *Studies II-IV*

Baseline SCr was measured at the time of admission to the ward, normally the day before surgery or within one week prior to surgery. The serum creatinine samples were analyzed at the laboratories of the eight different hospitals performing CABG.

## Classification of acute kidney injury

### *Study I and IV*

Acute kidney injury was classified according to the AKIN classification—stage 1: increase by SCr ≥26 μmol/L (≥0.3 mg/dL) or an increase by 50−100% of baseline SCr; stage 2: increase by 100−200% of baseline value; and stage 3: >200% increase of baseline SCr. In a complementary analysis for Study I, we also defined patients by the RIFLE stage 1 criteria: increase by 50−100% of baseline SCr.

### *Studies II and III*

Acute kidney injury was classified according to AKIN and another classification based on absolute increases of SCr. The division in absolute increases in SCr was based on the AKIN criteria and divided into three stages of AKI—stage 1: SCr increase of 26–44 μmol/L (0.3−0.5 mg/dL), stage 2: SCr increase of 44-88 μmol/L (0.5−1.0 mg/dL) and stage 3: SCr increase of ≥88 μmol/L (≥1.0 mg/dL) compared with the preoperative baseline SCr value.

## Definition of co-morbidities

Information on co-morbidities was collected from SWEDEHEART and NPR. Patients were defined as having hypertension if they were taking antihypertensive medication and defined as having DM if they had ongoing treatment with insulin or oral hypoglycemic agents. Peripheral vascular disease was defined as one or more of the following: claudication, carotid occlusion or >50% stenosis, amputation for arterial disease or previous or planned intervention on the abdominal aorta, limb arteries or carotids. Left ventricular function was measured by preoperative echocardiography or ventriculography. Ejection fraction (EF) was considered normal if >55%, reduced if EF was 30–55%, and severely reduced if <30%. Chronic kidney disease was defined as GFR <60 mL/min/1.73m$^2$ calculated by the MDRD equation. Stroke and MI were defined according to ICD codes from NPR.

### *Outcome measures*

Outcomes in Study I: short-term (*i.e.* 60 days) risk for all-cause mortality and postoperative stroke and mediastinitis; in Study II: long-term risk of all-cause mortality and MI; in Study III; long-term risk of stroke; and Study IV: long-term risk of ESRD or ESRD and death.

### *Follow-up*

In Study I, follow-up started when SCr was analyzed postoperatively to classify AKI. In 93% of samples, this occurred within 48 hours after surgery. Follow-up ended 60 days after surgery. Information on deceased patients was retrieved by linking the patients personal identity number to the Cause of Death register. Stroke was defined as central neurological symptoms persisting >72 hours. Mediastinitis was defined as a deep sternal wound infection requiring antibiotics and surgical intervention.

All-cause mortality was an outcome in all four studies. In Studies II−IV, information on deceased patients was obtained from the total population register.

In Study II, follow-up started at the date of surgery and ended when patients were discharged with a principal discharge diagnosis of MI defined by code I21 in ICD 10 (received from NPR), died, or until 31 December 2009, whichever occurred first.

In Study III, follow-up started 30 days after surgery and patients were followed until they were discharged with a principal diagnosis of any stroke (ICD I63.9, I61.9), died, or until 31 December 2008, whichever occurred first. Information on stroke vas obtained from NPR, where stroke has a positive predictive value of 98.6%.[149]

In Study IV, follow-up started 30 days after surgery and patients were followed until the date when they first appeared in the renal register, died, or until 31 December 2008, whichever occurred first.

## STATISTICAL ANALYSIS

### Study I

Baseline characteristics among the patients were presented with one standard deviation (SD) and percentages in the different AKIN stages and then compared between groups by calculating P–values using Mantel–Haentzels test. Logistic regression analysis was performed crude and after adjustment for potential confounders from patient characteristics to calculate odds ratios (OR) for mortality within 60 days of surgery among patients in AKIN stages 1 and stages 2–3 combined, compared with patients without AKI. The OR was presented with 95% CI. In the multivariable adjusted model, confounders that affected the OR >0.1 were included in the final model.

We also examined the ability of AKIN and RIFLE to identify early deaths by using ROC. AUCs were calculated and compared by nonparametric methods by Mann−Whitney and $\chi^2$ tests. SAS statistical software, version 9.2 (SAS Institute, Inc. Cary, NC) was used for all statistical analyses.

### Studies II - IV

Continuous baseline variables were presented using means and one SD. Categorical variables show percentages in relation to AKI group. Some values were missing from datasets in Studies II-IV, including left ventricular ejection fraction (in 7.7% of patients), information on diabetes mellitus (in 26%), and peripheral vascular disease (in 7.4%). Imputation by chained equations was used to handle missing baseline values for LVF and DM in Study II, DM and peripheral vascular disease in Study III and LVF, DM and peripheral vascular disease in study IV, thereby permitting multivariable adjustment for confounders in the whole cohort. The Kaplan–Meier method was used to calculate cumulative incidences of outcomes in relation to different AKI groups. Univariate and multivariable Cox regression analysis was used to handle confounding factors and calculate HR with 95% CI for outcomes among patients with AKI compared with patient without AKI. In Studies III and IV, we used competing risk regression analysis to handle death as a competing risk.

Stata version12.1 (StataCorp LP, College Station, TX, USA) was used for all analyses in Studies II and III; version 13.1 was used in study IV.

# RESULTS

## STUDY I

### Patient characteristics

Baseline characteristics of all patients in Study I are shown in Table 5. Over all, the incidence of AKI was 14%. Generally, patients with AKI were older, more likely to be female and suffered from more co-morbidities than did patients without AKI.

**Table 5. Preoperative characteristics of patients in Study I classified by Acute Kidney Injury Network (AKIN) classification stage*.**

| | All patients | No AKI | AKIN 1 | AKIN 2 | AKIN 3 |
|---|---|---|---|---|---|
| All patients (%) | 7594 (100) | 6547 (86.2) | 918 (12.1) | 108 (1.4) | 21 (0.3) |
| Women (%) | 1549 (20) | 1350 (21) | 174 (19) | 19 (18) | 6 (29) |
| Diabetes mellitus (%) | 1536 (20) | 1262 (19) | 247 (27) | 24 (23) | 3 (14) |
| Preoperative eGFR <60 mL/min/1.73m$^2$ (%) | 1361 (18) | 979 (15) | 358 (39) | 21 (19) | 3 (14) |
| LVF -Normal (%) | 4675 (62) | 4157 (63) | 461 (50) | 46 (43) | 11 (52) |
| -Decreased (%) | 2137 (28) | 1762 (27) | 322 (35) | 45 (42) | 8 (38) |
| -Severely Decreased (%) | 460 (6.1) | 362 (5.5) | 83 (9.0) | 13 (12) | 2 (9.5) |
| Unstable angina pectoris (%) | 3444 (45) | 2908 (44) | 465 (51) | 58 (54) | 13 (62) |
| Age, mean (SD), years | 65.5 (9.7) | 65.2 (9.7) | 68.5 (9.8) | 67.1 (9.6) | 68.2 (9.0) |
| Serum Creatinine, mean (μmol/L) (SD) | 92 (31) | 91 (26) | 114 (54) | 92 (29) | 83 (27) |

*AKIN, Stage 1: Increase in serum creatinine >0.3 mg/dL or a serum creatinine of 150–200% of baseline value. Stage 2: Serum creatinine of 200–300% of baseline value. Stage 3: Serum creatinine of >300% of baseline value. AKI, acute kidney injury; LVF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; SD, standard deviation. Numbers given with mean and standard deviations.

### Outcomes

### Early mortality

Of 7594 patients, 132 (1.7%) died during follow-up. The proportion of patients who died increased with increasing AKIN stage. The ORs for death within 60 days of surgery gradually increased, even after multivariable adjustment for several confounders. Compared with patients with no AKI, those in AKIN stage 1 had four times the risk for death and those

in stages 2–3 had 20-times the risk (Table 6). In a subgroup analysis of 2984 patients, we calculated ORs for short-term mortality and found that the high mortality risk persisted even after adjustment for timing of coronary angiography was included in the statistical model; its inclusion did not significantly change the OR values. Furthermore, we stratified patients according to eGFR above and below 60 mL/min/1.73m$^2$, and found similar results in both categories of renal function.

Comparison between AKIN and RIFLE by ROC analysis showed a better prediction of death with AKIN (AUC: AKIN, 0.74; RIFLE, 0.66; $P$ <0.01).

## Postoperative complications

Among patients without AKI, 1.0% developed a postoperative stroke and 1.1% mediastinitis. Among patients with AKI, 3.4% of those in AKIN stage 1 and 7.8% in AKIN stages 2+3 developed strokes. A similar association was found between AKI and mediastinitis (Table 6).

**Table 6. Incidence of mortality, stroke, and mediastinitis within 60 days of coronary bypass grafting in relation to acute kidney injury classified by Acute Kidney Injury Network (AKIN) stage*. Odds ratios were calculated relative to patients without acute kidney injury and presented with 95% confidence intervals.**

| | | AKIN stage | | |
|---|---|---|---|---|
| | All patients | No AKI | Stage 1 | Stage 2 and 3 |
| Number of patients | 7594 | 6547 | 918 | 129 |
| *Mortality* | 132 (1.7%) | 54 (0.82%) | 54 (5.9%) | 24 (19%) |
| Multivariable adjustment† | | 1.0 | 4.36 (2.83-6.71) | 21.5 (12.0-38.6) |
| Number of patients | 7568 | 6523 | 918 | 129 |
| *Stroke* | 103 (1.4%) | 62 (1.0%) | 31 (3.4%) | 10 (7.8%) |
| Multivariable adjustment† | | 1.0 | 2.34 (1.43-3.82) | 6.52 (2.97-14.3) |
| Number of patients | 7594 | 6547 | 918 | 129 |
| *Mediastinitis* | 118 (1.6%) | 74 (1.1%) | 36 (3.9%) | 8 (6.2%) |
| Multivariable adjustment† | | 1.0 | 2.88 (1.84-4.50) | 4.68 (2.07-10.6) |

*AKIN, Stage 1: Increase in serum creatinine (SCr) >0.3 mg/dL or SCr of 150–200%. Stage 2: SCr of 200–300%. Stage 3: SCr of >300%, all compared to baseline value. AKI, acute kidney injury; OR, odds ratio; CI, confidence interval. †Adjusted for; age, gender, preoperative estimated glomerular filtration rate, left ventricular function, diabetes mellitus, body mass index, unstable angina pectoris.

## STUDY II

### Patient characteristics

Patient characteristics are presented in Table 7. Their mean age was 67 years and 21% were women. In total, 13 % of these patients developed AKI after surgery. The largest percentage, 6.3% were in AKI stage 1, 4.3% in stage 2 and 2.3% in AKI stage 3. Of all 27 927 patients, 20% had eGFRs <60 mL/min/1.73m$^2$ before undergoing CABG. Patients with AKI had more co-morbidities than patients without AKI.

**Table 7. Characteristics of the study population in relation to acute kidney injury, classified by absolute increases in postoperative serum creatinine values*.**

| | All patients | No AKI | Stage 1 | Stage 2 | Stage 3 |
|---|---|---|---|---|---|
| Number of patients (%) | 27 929 (100) | 24 312 (87) | 1763 (6.3) | 1209 (4.3) | 645 (2.3) |
| Age, mean (SD), years | 67.1 (9.2) | 66.6 (9.2) | 70.0 (8.8) | 70.9 (8.8) | 71.2 (9.0) |
| Preoperative. eGFR mL/min/1.73m$^2$% | | | | | |
| eGFR >60 | 80 | 82 | 69 | 58 | 44 |
| eGFR 45–60 | 15 | 14 | 21 | 24 | 24 |
| eGFR 30–45 | 4 | 3 | 8 | 14 | 19 |
| eGFR 15–30 | 1.0 | 0.5 | 2 | 4 | 13 |
| Female sex, n (%) | 5967 (21) | 5229 (22) | 357 (20) | 252 (21) | 129 (20) |
| Preoperative SCr (SD), mg/dL | 1.0 (0.3) | 1.0 (0.3) | 1.1 (0.4) | 1.2 (0.5) | 1.5 (0.7) |
| EuroSCORE (SD) | 3.8 (2.5) | 3.7 (2.4) | 4.6 (2.5) | 5.0 (2.5) | 5.6 (2.6) |
| Prior MI, % | 42 | 40 | 46 | 51 | 55 |
| Prior hospitalization for CHF, % | 4 | 3 | 6 | 9 | 10 |
| Left ventricular function, % | | | | | |
| Ejection fraction >50% | 70 | 72 | 65 | 58 | 55 |
| Ejection fraction 30–50% | 26 | 25 | 30 | 35 | 35 |
| Ejection fraction < 30% | 4 | 4 | 5 | 6 | 9 |

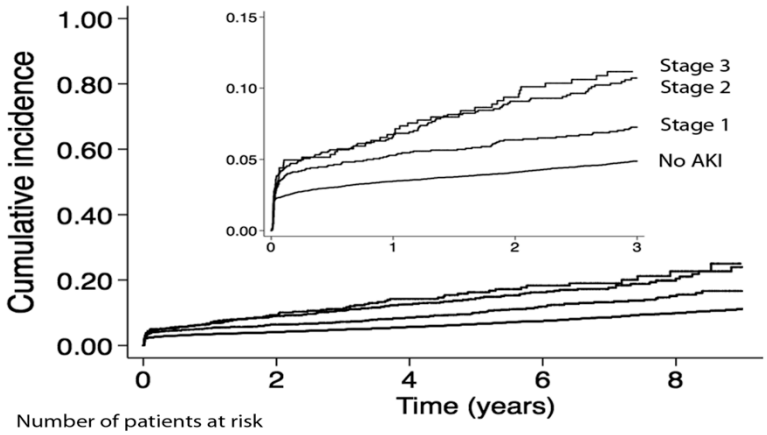
AKI, acute kidney injury; SD, standard deviation; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; CABG, coronary artery bypass grafting; EuroSCORE, European system for cardiac operative risk evaluation; MI, myocardial infarction; CHF, congestive heart failure. Age, and SCr values are given as means with standard deviations. *Acute kidney injury classified according to absolute raise in SCr values. Stage 1: 0.3–0.5 mg/dL. Stage 2: 0.5–1 mg/dL. Stage 3: >1 mg/dL.

## Outcomes

### Myocardial infarction and death

This population had 2119 (7.6%) myocardial infarctions and 4679 (17%) deaths over a mean follow-up period of 5.0 years, and showed increasing risk of MI with advancing AKI stage over time (Figure 2). Patients without AKI were more likely to be alive throughout the study period (Figure 3).

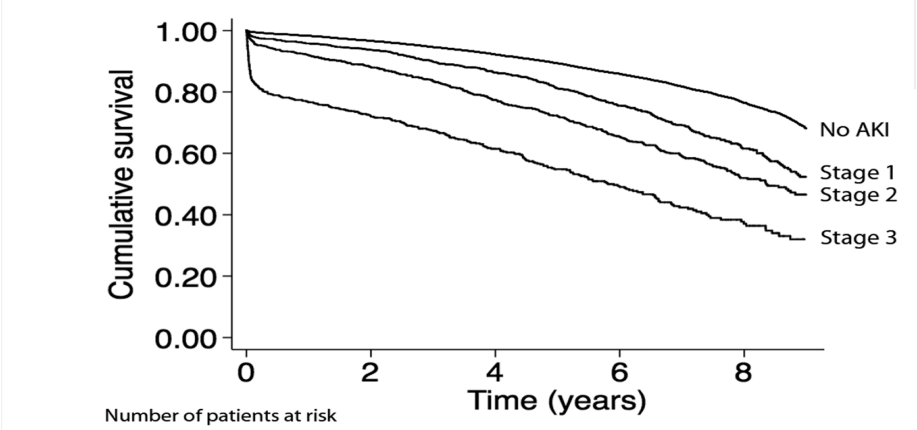
**Figure 2**. **Cumulative incidence of myocardial infarction in 27 929 patients who underwent primary isolated coronary artery bypass grafting in Sweden, 2000–2008. The inset shows the same data on a rescaled y-axis.**




Number of patients at risk

| | | | | | |
|---|---|---|---|---|---|
| No AKI | 24312 | 20341 | 14645 | 8571 | 3327 |
| Stage 1 | 1763 | 1376 | 968 | 556 | 205 |
| Stage 2 | 1209 | 850 | 574 | 331 | 130 |
| Stage 3 | 645 | 371 | 243 | 133 | 49 |

**Figure 3. Cumulative survival in 27 929 patients who underwent primary isolated coronary artery bypass grafting in Sweden, 2000–2008.**




Number of patients at risk

| | | | | | |
|---|---|---|---|---|---|
| No AKI | 24312 | 21096 | 15332 | 9053 | 3549 |
| Stage 1 | 1763 | 1460 | 1039 | 603 | 225 |
| Stage 2 | 1209 | 915 | 636 | 376 | 147 |
| Stage 3 | 645 | 407 | 265 | 150 | 55 |

The HR for MI is presented in Table 8. In an additional analysis, we excluded all patients who died (*n*=502) or had an MI (*n*=828) within 60 days of surgery and calculated HRs for death or MI during follow-up. After adjustment for confounders, the results were similar to the HRs for the cohort as a whole.

In addition, we performed a complete case analysis of only patients with no missing covariates, and found results to be similar to the analysis with imputed missing covariates.

**Table 8. Hazard ratios for myocardial infarction and all-cause mortality with 95% confidence intervals in relation to acute kidney injury stage defined by absolute increase in postoperative serum creatinine values*.**

| | No AKI† | Stage 1 | Stage 2 | Stage 3 |
|---|---|---|---|---|
| Number of patients (%) | 24 312 (87) | 1763 (6) | 1209 (4) | 645 (2) |
| *Myocardial infarction* | | | | |
| Number of MIs (%) | 1691 (7) | 181 (10) | 166 (14) | 81 (13) |
| Multivariable adjustment‡ | 1.00 | 1.35 (1.15–1.57) | 1.80 (1.53–2.13) | 1.63 (1.29–2.07) |
| *All-cause mortality* | | | | |
| Number of Deaths (%) | 3532 (15) | 427 (24) | 402 (33) | 318 (49) |
| Multivariable adjustment‡ | 1.00 | 1.30 (1.17–1.44) | 1.65 (1.48–1.83) | 2.68 (2.37–3.03) |

*Acute kidney injury classified according to absolute increase in serum creatinine values. Stage 1: 0.3–0.5 mg/dL. Stage 2; 0.5–1 mg/dL. Stage 3; >1 mg/dL. AKI, acute kidney injury; MI, myocardial infarction.
†Reference category.
‡Multivariable adjustment was made for: age, sex, diabetes mellitus, estimated glomerular filtration rate, left ventricular ejection fraction, prior MI, heart failure or stroke.

Sex-specific analysis showed that the relative risk for MI associated with AKI was similar in men and woman. When stratified by preoperative eGFR we saw a significant association between AKI and MI at all levels of renal function (Table 9).

**Table 9. Hazard ratios for myocardial infarction and all-cause mortality with 95% confidence intervals in relation to acute kidney injury stage defined by absolute increase in postoperative serum creatinine values* stratified by preoperative renal function in patients undergoing coronary bypass grafting.**

| | Acute Kidney Injury Stage | | |
|---|---|---|---|
| | No AKI† | 1 | 2 + 3 |
| *Myocardial infarction* | | HR (95% CI)‡ | HR (95% CI)‡ |
| GFR ≥60 mL/min/1.73 $m^2$ | 1.00 | 1.37 (1.12–1.66) | 1.82 (1.50–2.20) |
| GFR 45–60 mL/min/1.73 $m^2$ | 1.00 | 1.49 (1.09–2.04) | 1.90 (1.44–2.50) |
| GFR 15–45 mL/min/1.73 $m^2$ | 1.00 | 1.11 (0.70–1.76) | 1.40 (1.02–1.92) |
| *All-cause mortality* | | | |
| GFR ≥60 mL/min/1.73 $m^2$ | 1.00 | 1.29 (1.12–1.47) | 1.95 (1.72–2.21) |
| GFR 45–60 mL/min/1.73 $m^2$ | 1.00 | 1.27 (1.04–1.56) | 2.33 (1.99–2.73) |
| GFR 15–45 mL/min/1.73 $m^2$ | 1.00 | 1.35 (1.06–1.72) | 1.68 (1.40–2.00) |

*Acute kidney injury classified according to absolute increase in SCr values. Stage 1: 0.3–0.5 mg/dL. Stage 2: 0.5–1 mg/dL. Stage 3: >1 mg/dL.
† Reference category. GFR was estimated by the Modification of Diet in Renal Disease study equation.
AKI, acute kidney injury; GFR, glomerular filtration rate; HR, hazard ratio; CI, confidence interval.
‡Multivariable adjustment was made for age, sex, diabetes mellitus, left ventricular ejection fraction, prior myocardial infarction, prior heart failure, and prior stroke.

## STUDY III

### Patient characteristics

The exclusion criteria of patients in study III are presented in Figure 1. Baseline characteristics of the population in Study II and Study III was similar (Table 7).

### Outcomes

During a mean follow-up period of 4.1 years, 1156 (4.9%) patients had a first stroke. Most of these, 73% were ischemic, 8% were hemorrhagic, and 19% unspecified. The mean time to a first stroke was 2.9 years. The risk of stroke increased with increasing AKI stage (Table 10).

**Table 10. Hazard ratios of first hospitalization for all strokes, ischemic or hemorrhagic stroke with 95% confidence intervals in relation to acute kidney injury, classified according to absolute increase in serum creatinine values*, in 23 584 patients undergoing primary isolated coronary bypass grafting, 2000–2008 in Sweden.**

| | Acute Kidney Injury Stage | | | |
|---|---|---|---|---|
| | No AKI† | 1 | 2 | 3 |
| Number of patients | 20 820 | 1404 | 944 | 416 |
| *All strokes* | | | | |
| Number of events (%) | 959 (5) | 87 (6) | 77 (8) | 33 (8) |
| Incidence rate (per 1000 PY) | 11 (10–12) | 16 (13–19) | 21 (17–26) | 23 (17–32) |
| Multivariable adjustment‡ | 1.00 | 1.12 (0.89–1.39) | 1.31 (1.04–1.66) | 1.31 (0.92–1.87) |
| *Ischemic stroke* | | | | |
| Number of events (%) | 694 (3) | 67 (5) | 52 (6) | 25 (6) |
| Incidence rate (per 1000 PY) | 8 (7–9) | 12 (9–15) | 14 (11–19) | 17 (12 -25) |
| Multivariable adjustment‡ | 1.00 | 1.18 (0.92–1.52) | 1.21 (0.91–1.61) | 1.37 (0.91–2.05) |
| *Hemorrhagic stroke* | | | | |
| Number of events (%) | 85 (0.4) | 7 (0.5) | 6 (0.6) | 4 (1) |
| Incidence rate (per 1000 PY) | 1 (0.8–1.2) | 1.2 (0.6–2.5) | 1.6 (0.7–3.5) | 2.6 (1–7) |
| Multivariable adjustment‡ | 1.00 | 1.02 (0.47–2.22) | 1.13 (0.49–2.62) | 1.75 (0.63–4.91) |

*Acute kidney injury (AKI) classified according to absolute increase in SCr values. Stage 1: 0.3–0.5 mg/dL. Stage 2: 0.5–1 mg/dL. Stage 3: >1 mg/dL.
†Reference category.
PY, person years.
‡Multivariable adjustment was made for age, sex, preoperative estimated glomerular filtration rate, atrial fibrillation, diabetes mellitus, peripheral vascular disease, and preoperative heart failure.

The cumulative incidence of stroke 5 years after CABG was 8.0% among patients in AKI stage 1, 9.9% in stage 2 and 11% in stage 3. After multivariable adjustment for confounders, only patients in AKI stage 2 had a significantly increased risk of stroke (Table 10).

When AKIN criteria were used to classify patients with AKI, the associations were similar to analyses that used with absolute changes in SCr values (Table 11).

**Table 11. Hazard ratios of first hospitalization for all stroke, ischemic or hemorrhagic stroke with 95% confidence intervals in relation to acute kidney injury stage defined by the Acute Kidney Injury Network (AKIN) classification* in 23 584 patients undergoing primary isolated coronary artery bypass grafting in Sweden, 2000–2008.**

| | No kidney injury† | AKIN Stage 1 | AKIN Stage 2 | AKIN Stage 3 |
|---|---|---|---|---|
| Number of patients | 20 810 | 2449 | 273 | 52 |
| *All stroke* | | | | |
| Number of events (%) | 959 (4) | 175 (7) | 18 (7) | 4 (8) |
| Incidence rate (per 1000 PY) | 11 (10–12) | 18 (16–21) | 19 (12–30) | 21 (8–56) |
| Multivariable adjustment‡ | 1.00 | 1.20 (1.02–1.42) | 1.30 (0.81–2.07) | 1.55 (0.58–4.15) |
| *Ischemic stroke* | | | | |
| Number of events (%) | 694 (3) | 127 (5) | 14 (5) | 3 (6) |
| Incidence rate (per 1000 PY) | 8 (7–9) | 13 (11–16) | 14 (9–24) | 16 (5–48) |
| Multivariable adjustment‡ | 1.00 | 1.19 (0.98–1.45) | 1.36 (0.80–2.32) | 1.64 (0.53–5.11) |
| *Hemorrhagic stroke* | | | | |
| Number of events (%) | 85 (0.4) | 15 (0.6) | 2 (0.1) | 0 |
| Incidence rate (per 1000 PY) | 1 (0.8–1.2) | 1.5 (0.9–2.5) | 2 (0-5–8) | 0 |
| Multivariable adjustment‡ | 1.00 | 1.15 (0.66–2.02) | 1.58 (0.39–6.46) | - |

*Acute kidney injury classified according to the Acute Kidney Injury Network classification. Stage 1: 0.3–0.5 mg/dL or 50–100%. Stage 2: 0.5–1 mg/dL or 100–200%. Stage 3: >1 mg/dL or >200% increase from baseline.
†Reference category. PY, person years.
‡Multivariable adjustment was made for age, sex, preoperative estimated glomerular filtration rate, atrial fibrillation, diabetes mellitus, peripheral vascular disease, and preoperative heart failure.

When patients were stratified by sex and AKI dichotomized yes (>26 μmol/L increase in postoperative SCr) or no (<26 μmol/L increase in postoperative SCr), we found that the association between AKI and stroke was significant for men but not for women. When we stratified patients by preoperative eGFR in subgroup analyses, we found a significant association between AKI and stroke in patients with eGFR >60 mL/min/1.73m$^2$, but not between AKI and stroke in patients with CKD (Table 12).

**Table 12. Hazard ratios of all stroke and a composite end-point of all stroke or death with 95% confidence intervals in relation to acute kidney injury (yes/no), stratified by preoperative renal function in 23 584 patients who underwent primary isolated coronary artery bypass grafting in Sweden, 2000–2008.**

| | Acute Kidney Injury | |
|---|---|---|
| | No* | Yes |
| All stroke | | Hazard ratio (95% CI) |
| GFR ≥60 mL/min/1.73 $m^2$ | 1.00 | 1.26 (1.02–1.54) |
| GFR 45–60 mL/min/1.73 $m^2$ | 1.00 | 0.98 (0.70–1.36) |
| GFR 15–45 mL/min/1.73 $m^2$ | 1.00 | 1.26 (0.86–1.85) |
| | | |
| All stroke or death | | |
| GFR ≥60 mL/min/1.73 $m^2$ | 1.00 | 1.30 (1.17–1.44) |
| GFR 45–60 mL/min/1.73 $m^2$ | 1.00 | 1.56 (1.35–1.82) |
| GFR 15–45 mL/min/1.73 $m^2$ | 1.00 | 1.48 (1.23–1.77) |

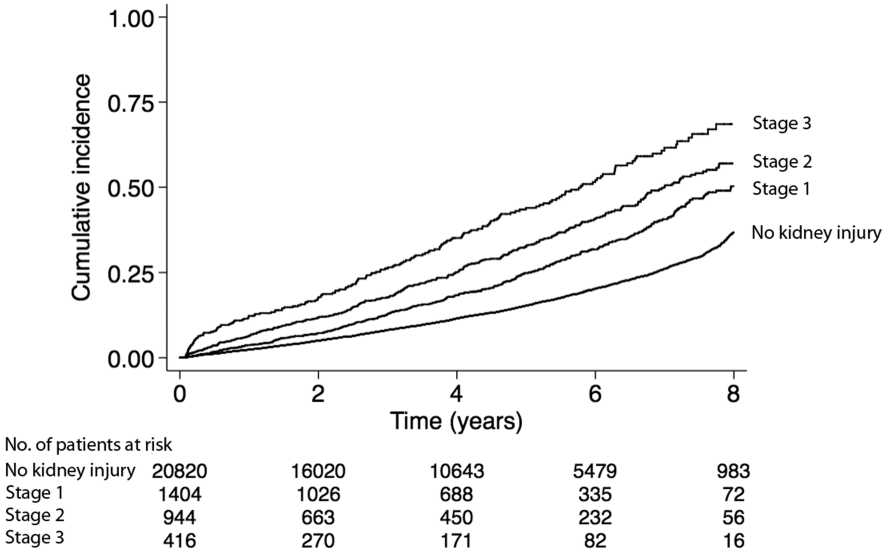
*Reference category. Acute kidney injury was defined as a postoperative increase in creatinine >26 μmol/L (0.3 mg/dL) compared with preoperative creatinine. Multivariable adjustment was made for age, sex, atrial fibrillation, diabetes mellitus, peripheral vascular disease, and preoperative heart failure. Glomerular filtration rate was estimated by the Modification of Diet in Renal Disease study equation.

Similarly, when we stratified into patients into those younger and older than 65 years and dichotomized those with and without AKI, we found a 57% increased risk for stroke among younger patients with AKI (HR: 1.57; 95% CI: 1.12–2.22).

### *Composite end-point of death and stroke*

An association was found between AKI and the cumulative end-point stroke or death over 8 years after undergoing CABG (Figure 4). When we dichotomized patients into presence or absence of AKI and calculated adjusted HRs for death or stroke, we found risk increased by 1.51 (95% CI: 1.40–1.63).

**Figure 4. Cumulative incidence of stroke or death in relation to the stage of acute kidney injury, classified according to absolute increase in serum creatinine values, in patients undergoing primary isolated coronary artery bypass grafting in Sweden from 2000-2008.**




### *Competing risk*

As death might be a competing risk for stroke, we analyzed the association between AKI and stroke with competing risk regression. The subhazard ratio for stroke was non-significant over all stages of AKI. This indicates that death indeed is a competing event for stroke.

## STUDY IV

### Patient characteristics

The population in Study IV was recruited from the SWEDEHEART register and included all patients who underwent a primary, isolated CABG during 2000 to 2008, in Sweden, for a total of 29 330 patients. Their baseline characteristics are shown in Table 13.

**Table 13. Baseline characteristics by level of acute kidney injury according to the Acute Kidney Injury Network classification*.**

| | | Acute Kidney Injury stage | | |
|---|---|---|---|---|
| | All patients | 0 | 1 | 2 and 3 |
| Number of patients (%) | 29 330 (100) | 25 609 (87) | 3159 (11) | 562 (1.9) |
| Age (SD), years | 67.0 (9.2) | 66.5 (9.2) | 70.5 (8.8) | 69.7 (9.2) |
| eGFR mL/min/1.73 $m^2$, % | | | | |
| eGFR >60 | 80 | 83 | 63 | 62 |
| eGFR 45–60 | 15 | 14 | 23 | 18 |
| eGFR 30–45 | 4.2 | 3.1 | 12 | 10 |
| eGFR 15–30 | 0.9 | 0.4 | 2.7 | 11 |
| Female sex, % | 21 | 21 | 20 | 23 |
| eGFR (SD), mL/min/1.73 $m^2$ | 77 (21) | 78 (20) | 69 (23) | 71 (33) |
| Preoperative SCr (SD), μmol/L | 92 (26) | 90 (22) | 104 (34) | 114 (65) |
| EuroSCORE (SD) | 3.9 (2.5) | 3.7 (2.4) | 4.9 (2.5) | 5.2 (2.7) |
| Diabetes mellitus, % | 23 | 22 | 31 | 32 |
| Prior hospitalization for CHF, % | 3.7 | 3.2 | 7.1 | 7.3 |
| Left ventricular function, % | | | | |
| Ejection fraction >50% | 70 | 71 | 62 | 55 |
| Ejection fraction 30–50% | 26 | 25 | 32 | 38 |
| Ejection fraction <30% | 3.7 | 3.3 | 5.8 | 7.8 |
| Internal thoracic artery use, % | 94 | 94 | 94 | 94 |
| CABG without cardiopulmonary bypass, % | 5.4 | 5.2 | 6.4 | 7.5 |

SD, standard deviation; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; CHF, congestive heart failure; CABG, coronary artery bypass grafting. Age, eGFR, serum creatinine, and EuroSCORE values are given as means with standard deviations.

*Classification system for acute kidney injury. Serum creatinine criteria. Stage 1: Increase in serum creatinine of ≥0.3 mg/dL (≥26.4 μmol/L) or increase to ≥150–200% from baseline. Stage 2: Increase in serum creatinine to >200–300% from baseline. Stage 3: Increase in serum creatinine to >300% from baseline (or serum creatinine of ≥4.0 mg/dL [≥354 μmol/L] with an acute increase of >0.5 mg/dL [44 μmol/L]). Patients who receive renal replacement are considered to have met the criteria for stage 3.

We excluded 9969 patients whose SCr information was missing (Figure 1), although their 1-, 5- and 10-year survival did not significantly differ from patients with information on SCr.

## Outcomes

### *End-stage renal disease and mortality*

During a mean follow-up period of 4.3 years, 123 (0.4%) patients developed ESRD. The mean age of these patients when they started dialysis/were transplanted was 68 ±10 years. They had lower eGFRs, were more frequently diabetics and had reduced LVEF more often than patients who did not develop ESRD. Among patients without AKI, 0.2% (44) developed ESRD during follow-up. Among patients with AKI, 1.6% (50) of those at AKIN stage 1, and 5.2% (29) at AKIN stages 2–3, started treatment for ESRD during follow-up (Table 14). After multivariable adjustment for all baseline characteristics in Table 13, HR for ESRD among patients at AKIN stage 1 was almost three times higher, and the risk for patients without AKI (Table 14). For patients at AKIN stages 2–3, the risk was almost four times higher.

**Table 14. Association between acute kidney injury, using the Acute Kidney Injury Network (AKIN) classification* and risk for end-stage renal disease (ESRD) and ESRD or death in 29 330 patients who underwent primary isolated coronary artery bypass grafting in Sweden, 2000–2008.**

| | 0† | AKIN Stage 1 | AKIN Stage 2 and 3 |
|---|---|---|---|
| Number of patients (%) | 25 609 (87) | 3159 (11) | 562 (1.9) |
| *ESRD* | | | |
| Number of events (%) | 44 (0.2) | 50 (1.6) | 29 (5.2) |
| Multivariable adjusted‡ HR (95% CI) | 1.00 | 2.92 (1.87–4.55) | 3.81 (2.14–6.79) |
| *ESRD + death* | | | |
| Number of events (%) | 3554 (14) | 840 (27) | 216 (38) |
| Multivariable adjusted‡ HR (95% CI) | 1.00 | 1.34 (1.23–1.45) | 2.32 (2.01–2.68) |

*Classification system for acute kidney injury. Serum creatinine (SCr) criteria. Stage 1: Increase in SCr of ≥0.3 mg/dL (≥26.4 μmol/L) or increase to ≥150–200% from baseline. Stage 2: Increase in SCr to >200% to 300% from baseline. Stage 3: Increase in SCr to >300% from baseline (or SCr of ≥4.0 mg/dL [≥354 μmol/L] with an acute increase of at least 0.5 mg/dL [44 μmol/L]). Patients who receive renal replacement are considered to have met the criteria for stage 3. HR, hazard ratio
†Reference category. All *P*-values for Acute Kidney Injury stage 1 and 2–3 *vs*. AKI stage 0 were <0.001.
‡Multivariable adjustment was made for all variables in Table 13.

Figure 5 describes the cumulative incidence of ESRD, taking death into account as a competing event. The cumulative incidence of ESRD increased as AKIN stage advanced.

Figure 6 describes the cumulative incidence of the combined outcome of ESRD and death during 8 years of follow-up.

**Figure 5. Cumulative incidence of end-stage renal disease using the Acute Kidney Injury Network (AKIN) classification of acute kidney injury (AKI) in 29 330 patients who underwent primary isolated coronary artery bypass grafting in Sweden, 2000–2008.**

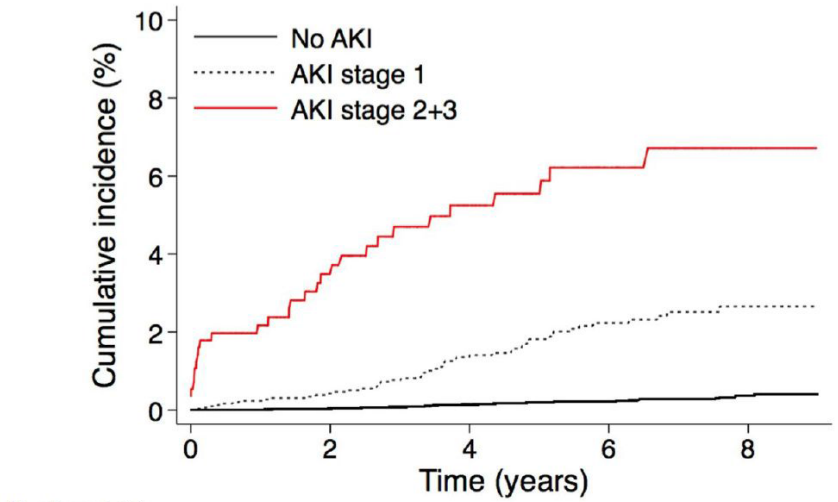
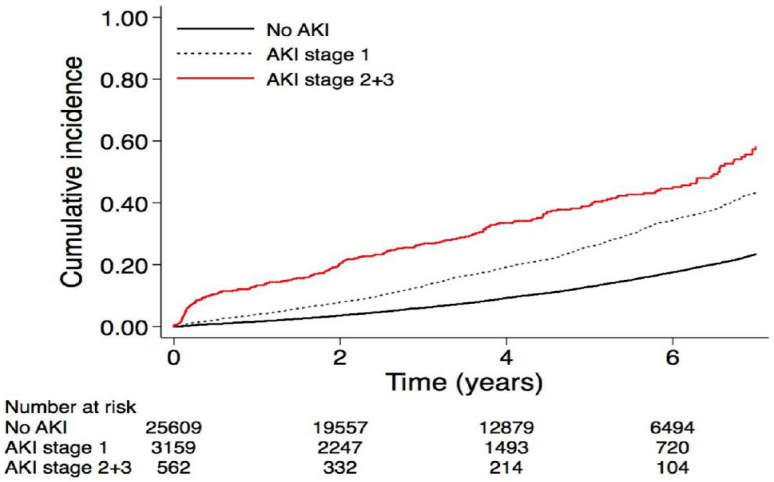



**Figure 6. Cumulative incidence of end-stage renal disease or death, using the Acute Kidney Injury Network (AKIN) classification for acute kidney injury (AKI) in 29 330 patients who underwent primary isolated coronary artery bypass grafting in Sweden, 2000–2008.**



In a subgroup analysis, we stratified patients by preoperative renal function. The adjusted HR for ESRD, among patients with AKI compared with patients without AKI, is shown in Table 15. Patients with a normal preoperative eGFRs who developed AKI postoperatively had a six-fold increase in risk of developing ESRD during follow-up. The risk for development of ESRD was higher among patients with preoperative eGFR >60 mL/min /1.73m$^2$ than among patients with worse eGFRs. The corresponding HR for ESRD and death in different groups of preoperative kidney function showed increased risk for developing ESRD of 30–70% in all patients with AKI, compared with patients without AKI (Table 15).

**Table 15. Association between acute kidney injury (yes/no) and end-stage renal disease (ESRD) and ESRD or death stratified by preoperative renal function in 29 330 patients who underwent primary isolated coronary artery bypass grafting during 2000 to 2008 in Sweden.**

| | Acute Kidney Injury | |
|---|---|---|
| | No* | Yes |
| *ESRD* | | Hazard Ratio (95% CI) |
| GFR ≥60 mL/min/1.73 m$^2$ | 1.00 | 6.24 (1.94–20.1) † |
| GFR 45–60 mL/min/1.73 m$^2$ | 1.00 | 4.54 (2.00–10.3) † |
| GFR 15–45 mL/min/1.73 m$^2$ | 1.00 | 3.48 (2.17–5.57) † |
| *ESRD or death* | | |
| GFR ≥60 mL/min/1.73 m$^2$ | 1.00 | 1.32 (1.19–1.46) ‡ |
| GFR 45–60 mL/min/1.73 m$^2$ | 1.00 | 1.72 (1.50–1.98) ‡ |
| GFR 15–45 mL/min/1.73 m$^2$ | 1.00 | 1.55 (1.32–1.83)‡ |

Acute kidney injury was defined as Acute Kidney Injury Network stage 1 or higher. GFR was estimated by the Modification of Diet in Renal Disease study equation. There was no evidence for a significant renal function by acute kidney injury interaction for the outcomes ESRD ($P$=0.523) or ESRD/death ($P$=0.080).
*Reference category
†Multivariable adjustment was made for age, sex, diabetes, and peripheral vascular disease.
‡Multivariable adjustment was made for age, sex, diabetes, peripheral vascular disease, left ventricular function, chronic obstructive pulmonary disease, atrial fibrillation, history of heart failure, prior myocardial infarction, prior stroke, and use of an internal mammary artery.

When patients were stratified for sex, adjusted HR for ESRD was 2.97 (95% CI: 1.85–4.78) in men and 3.51 (95% CI: 1.46–8.40) in women.

# DISCUSSION

## METHODOLOGICAL CONSIDERATIONS

Through epidemiologic research, we can describe the occurrence of diseases, the effects of treatments, and compare treatments and preventive actions. All epidemiological studies are affected by systematic error (bias) and random error to some extent, but if the researcher is aware of this, the effects of bias can be handled and their influence can be minimized.

### Study design

For an epidemiologist, studying the entire world's population would be fantastic, but of course, this is not possible. Instead, the epidemiologist must define a group of individuals who are representative of the background population. There are different types of epidemiological study designs. They can be divided into two main types; intervention (experimental) and observational (descriptive or analytic) studies. Interventional studies, i.e., Randomized Clinical Trials (RCTs) are considered superior to other types of studies because of the control of the exposure and preferably an even distribution of confounders in both exposed and non-exposed subjects. However, well-designed observational studies have been shown to be at least as valid as randomized trials.[153, 154] Furthermore, conducting a RCT is not possible in some situations. In addition, RCTs are associated with high costs. In Sweden, we have numerous registers with high validity, and our unique personal identity numbers facilitate gathering and merging information from several registers into a study cohort.

Observational studies can be further divided into longitudinal and cross sectional studies, which in turn represents case-control, cohort and ecological studies. This thesis contains cohort studies.

## Systematic error

Another word for systematic error is 'bias', meaning 'deviation from the truth'.[155] Bias is not dependent on chance, but rather reflects shortcomings in the study design. Bias can be divided into selection bias, information bias and confounding. Different types of bias affect the internal validity of a study. Systematic error cannot be handled by increasing the size of the study population. Only a well-designed study can reduce the effect of systematic error. Since observational studies aren't randomized, with equal distributions of patients within different groups, considering other explanations that can affect the results is essential.[156]

## Selection bias

Selection bias is a systematic error that causes difficulties when subjects included in the study differ from those not included and can lead to over- or underestimation of the true relative risk.[156] In retrospective cohort studies, bias can arise if the study population is not well defined and individuals are excluded because of death or emigration before the beginning of follow-up.

In Study I, the study population was collected from a local register at the Karolinska University Hospital in Solna. Patients with missing SCr values were excluded from the study. Bias could be introduced if patients with missing SCr values were different from those with information on SCr values. We investigated the mortality among these individuals and found no difference in mortality.

## Information bias

Information bias is another type of systematic error. It is also called observation, classification, or measurement bias. It arises when information gathered from or about the study participant is incorrect.[156] An example of this misclassification would be an exposed patient with AKIN stage 3 being classified as having AKIN stage 1, in a study that used exposure as a defined category. Misclassification of study participants for either exposure or disease can be further divided into differential and non-differential misclassification. Differential misclassification arises when the misclassification of exposure is different for those with, compared to those without the disease. Misclassification is non-differential if it is unrelated to exposure; that is, the misclassification arises among both exposed and unexposed

subjects.[156] Thus non-differential misclassification tends to reduce differences between groups, whereas differential misclassification tends to over-or underestimate their differences.[155, 156]

Information bias can also be introduced when patients with missing values are excluded from a study. As an example, 26% of the patients in our cohort had missing information on DM. After multiple imputation of this variable, we found similar HRs for outcomes in question in groups with and without information on DM, which indicates that the missing information on DM was missing at random.

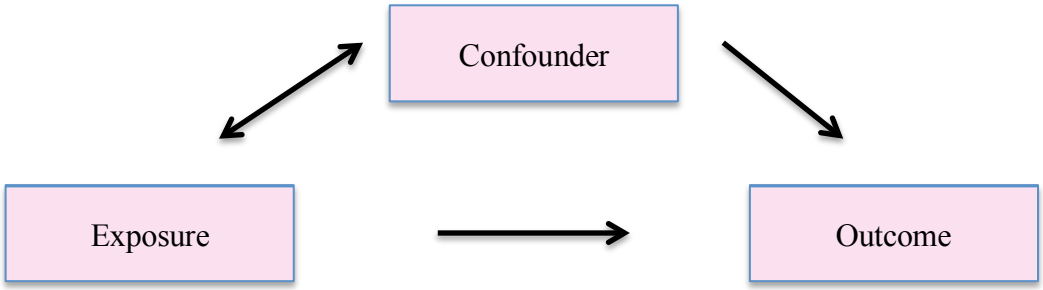
Potentially, AKI has a risk of misclassification in all our studies. AKIN, RIFLE and absolute increase of SCr all depend on changes in SCr, but SCr is a surrogate marker for kidney injury. It is a marker for kidney function, but altered kidney function can be a physiological response, rather than a reflection of pathology; SCr can be increased by causes other than AKI. An example is hypovolemia, which can lead to a misclassification; a patient might be classified as having AKI if volume depletion (rather than kidney injury) is causing higher SCr levels. Another common origin of AKI misclassification among patients with missing baseline SCr levels is estimating SCr by the patients' weight and age, using the MDRD formula.[28] This method was not used in any of the studies included in this thesis; instead we excluded patients with missing baseline SCr levels. We also analyzed baseline characteristics of patients in Study IV with missing baseline information about SCr, post-operative SCr and DM status, in terms of 1-, 5-, and 10-year survival, and found no differences. So by excluding patients with missing SCr we have most probably not introduced any misclassification in the study. Since the study cohort is virtually the same in Studies II, III and IV, these results should be applicable to these studies as well.

Some outcomes in our studies might have been misclassified. Overall mortality as an outcome is hard to misclassify, as it is an irreversible state and virtually no information concerning death is missing, whereas MI and stroke outcomes in Studies II and III have some possibility of misclassification. Diagnosis of MI in Sweden has been evaluated in several studies and shown to have a high validity.[148, 157] Diagnosis of stroke as the principal cause of hospitalization has a positive predictive value of 94%.[158] Despite high quality registers, some patients may suffer misclassified MIs, strokes or transitory ischemic attacks, leading to bias in our results.

## Confounding

A confounder is a factor that is associated with both the exposure and the outcome studied (Figure 7.). It can be described as "confusion of effects".[156]

**Figure 7. A confounder is associated with the exposure and the outcome, but is not a part of the causal link.**




A major task in epidemiologic studies is controlling for confounding factors, which may be done by several methods, including randomizing, matching or restriction of study subjects, or stratifying or adjusting for confounders in multivariable regression analysis.[156] Confounding was controlled by using multivariable regression analyses in the studies in this thesis.

In study I, we had no information on smoking status, which could be a potential confounder. In general surgery, smoking is known to lead to adverse postoperative outcomes, such as impaired wound healing and increased mortality risk, whereas smoking cessation reduces postoperative adverse outcomes.[159] The same principle might be supposed of wound healing in CABG patients as in patients undergoing general surgery. Studies of smoking habits and cardiac surgery outcomes are limited, but increased risk for sternocutaneous fistulas and mediastinitis after sternal incision has been reported for smokers.[160] Other risk factors for mediastinitis are obesity and DM, for which we adjusted for in multivariable analysis.[160, 161]

We had no information on the use of intra-aortic balloon pumps, which potentially may have affected our results. However, as we excluded patients undergoing emergency surgery, this is unlikely to have affected our results. Another potential confounding factor could be operation time and cross clamp time, which we did not have information about. However, we

had information on number of peripheral anastomoses, which was not associated with the exposure or the outcome.

All our studies may be influenced by residual confounding factors not known to us. For example, we did not have information on preoperative proteinuria, some patients may have had normal eGFR with proteinuria. Another confounding factor in our studies might be the absence of information on potential nephrotoxic drugs such as NSAIDs or ACE inhibitors, which might affect the risk of AKI.

## Random error

Random error is the influence of chance. It affects the precision of estimates and is present in all studies. Random error is inversely proportional to sample size; increasing sample size tends to reduce random error. We used *P*-values and CIs to address the effect of random error. Confidence interval gives a range which is likely to include the true population value. *P*-values show the probability that the observed value is based on chance, given that the null hypothesis is true. If the *P*-value is set to <0.05, it means that there is less than 5% risk that our estimate is caused by chance.[156] A non-significant *P*-value doesn't necessary mean that the null hypothesis is true; the results should always be interpreted with caution.

## External validity

External validity or generalizability is the ability to apply results from one study to other cohorts, in other cities or countries than where the study was conducted. So what is the external validity of our studies? Our first study is a single-center study among patients who underwent primary isolated CABG, which may have affected its external validity. In Studies II–IV, the cohort consisted of all patients who underwent non-emergent CABG all over Sweden. However, our cohort is similar to other cohorts of patients undergoing CABG in both the United States and United Kingdom, in terms of ages and comorbidities,[14, 162] therefore we believe that our results are generalizable to other hospitals in other countries, with similar levels of health care.

## Causation

As this thesis is based on epidemiological studies, we studied AKI as exposure and investigated its association to different outcomes. We were not able to distinguish whether AKI caused the outcomes, or was merely a marker for increased risk of adverse outcome.

Few RCTs have addressed this subject but several epidemiological studies suggest an association between AKI and ESRD.[82, 163, 164] There are also some studies on animal models that suggest a causal relationship between AKI and long-term worsening of kidney function caused by microvascular damage, reduced capillary density, and chronic renal hypoxia.[165-167] In 2014, Garg *et al*. published a RCT that evaluated the association between AKI and kidney function 1 year after on- or off-pump CABG. Acute kidney injury was defined as a postoperative increase of SCr levels by >50% compared with preoperative levels. Fewer patients operated off-pump (18%) developed postoperative AKI than did patients operated on-pump (21%). However, at one year, the groups did not differ in kidney function.[168] This suggests that AKI is a marker for an increased risk of worsening of renal function rather than a causative factor in itself.

Several studies show a strong association between AKI and CKD; however, the RCT by Garg *et al*. found no difference between AKI and non-AKI patients after one year.[168]

However, the mechanism behind AKI and its relation to ESRD development is most likely multifactorial. It can be a proxy for a more complicated postoperative course or a more vulnerable group of patients with more advanced arteriosclerosis. The surgery can affect the kidneys and speed up and exacerbate decline in kidney function over time. AKI and ESRD also share several risk factors, including DM, older age, and hypertension.

# INTERPRETATION OF FINDINGS

## STUDY I: EARLY MORTALITY AND POSTOPERATIVE COMPLICATIONS IN RELATION TO AKI AFTER CABG

In Study I, we investigated the effect of AKI in postoperative complications and mortality within 60 days of a first isolated CABG. The 14% of these patients who were affected by AKI had increased mortality of more than 4 times that of patients without AKI. The risk for postoperative complications was also strongly associated with AKI.

The reported incidence of AKI in cardiac surgery patients varies from about 9% to 39%, depending on type of cardiac surgery, classification of AKI, and patient population.[61, 169, 170] Compared with other studies of patients who underwent non-emergent CABG, the incidence in our cohort is in the lower range, 14%. In another study by Li *et al*., AKI incidence was 20%, which may have been caused by 56% of the study population being diabetic, compared with 20% in our study. Their study population was also older. Furthermore, patients with dialysis-dependent renal failure were not excluded and baseline eGFR was lower than in our population.[43] In other cohorts of CABG patients in the United States, and United Kingdom AKI incidence was 11% and 12%, respectively. Even increases less than 26 μmol/L in postoperative SCr levels have been associated with early adverse outcome in a few studies.[20, 171, 172]

When we compared the predictive ability of AKI classified by AKIN and RIFLE, AUCs were 0.77 for AKIN 1 and 0.66 for RIFLE R ($P$ <0.01), indicating that AKIN is a better predictor of death in the short term than RIFLE.

Our data indicate that even very small increases in postoperative SCr levels should be taken seriously; this group of patients might benefit from closer postoperative surveillance.

## STUDY II: ACUTE KIDNEY INJURY FOLLOWING CABG AND LONG-TERM RISK OF MYOCARDIAL INFARCTION AND DEATH

In Study II we found a strong association between AKI and MI during a mean follow-up period of 5 years. Also, mortality during follow up was markedly increased, up to >3 times among patients with AKI stage 3. Our results are consistent with another study of patients who underwent primary isolated CABG, where AKI (as defined by RIFLE) was present in 12% of the study population and all-cause mortality rate was 22% among patients in RIFLE stage 1 at 5 years after surgery.[173] Hobson *et al*. presented a much higher incidence of AKI among isolated CABG patients—37% according to RIFLE—but the 5-year mortality among patients without AKI were similar, 14% among all patients who underwent cardiac surgery and 15% in our study.[45] Li *et al*. studied elective CABG patients and classified AKI according to AKIN. After 5 years, 20% of patients in AKIN stage 1 had died, as did ~40% of those in AKIN stage 2, and all patients in AKIN stage 3. Notably, 12% of the patients were older than 80 years, and 35% were older than 75 years, which might have contributed to the high mortality rates.

During follow-up, 2119 patients (7.6%) presented with MI. We found AKI stage 1 through 3 to be associated with a 35% to 63% increased risk of MI. In other studies concerning survival after CABG and cardiac events, without knowledge on AKI, the incidence of MI and all-cause mortality is slightly higher than ours.[174, 175] To the best of our knowledge, no previous study has investigated the association between MI and AKI. Although unknown confounders might cause part of the association, after controlling several important confounders, risk for MI among patients with AKI after CABG increased by 35% in AKI stage 1 compared with patients without AKI. This patient category might benefit from close surveillance by a cardiologist postoperatively to optimize all modifiable factors to prevent future cardiovascular disease.

## STUDY III: ACUTE KIDNEY INJURY AND LONG-TERM RISK OF STROKE AFTER CABG

Study III investigated the effect of AKI after CABG on long-term risk of stroke. We found a weak association between AKI and stroke, but the association disappeared after taking death into account as a competing risk.

As this cohort is generally the same as in Study II the overall incidence of AKI was 12%. The incidence of stroke during follow-up was almost 5%. In a previous study of patients treated with in-hospital dialysis, Wu *et al*. found increased risk of stroke over 3.4 years of follow-up, of 6.6 per 1000 person-years compared with 11.5 per 1000 person-years among patients without need of in-hospital dialysis.[176] These numbers are in line with our results.

A possible explanation of the pathogenesis linking kidney injuries to strokes has been described in a mouse model. Ischemic AKI was shown to cause damage of the blood–brain barrier and increase microvascular permeability in the brain and induction of pro-inflammatory chemokines.[177] Although the association between AKI and stroke disappeared after competing risk analysis, an association was seen between AKI and stroke among patients under the age of 65 years in age-stratified analysis.

Studies I, II and IV, as with many other studies on the subject, present significant associations between AKI and adverse outcomes—mainly short- and long-term mortality and risk for MI and ESRD. Interestingly, this study is not in line with those results, which might reflect different pathophysiological associations between those outcomes and cerebrovascular events. As discussed earlier, pathophysiological changes are found in mice with AKI and significant association is found among general hospitalized patients with dialysis-dependent AKI.[176, 177] A possible explanation is that this reflects competing insults, as patients develop stroke later in life (mean respective ages: 74 and 80 years for men and women), compared with MI (62 and 73 years) and may thus die before developing a cerebral insult.[178, 179]

## STUDY IV: ACUTE KIDNEY INJURY FOLLOWING CABG AND LONG-TERM RISK OF END-STAGE RENAL DISEASE

Study IV investigated the effect of AKI after a first isolated CABG and development of ESRD. We found a strong association between AKI and development of ESRD that persisted after adjustment for several confounders. Among patients with AKIN 1 the HR for ESRD was more than twice that of patients without AKI, and tripled for patients with AKIN 2–3. Incidence rate of ESRD was 0.40 (95% CI: 0.30–0.53) per 1000 person-years among patients without AKI and 3.68 (2.79–4.86) and 13.2 (9.14–18.9) among patients in AKIN 1 and 2+3 combined.

No studies are available on ESRD development in patients with AKI who have undergone a first isolated CABG, although associations between AKI and progression in CKD stage or

development of ESRD has been described in several other clinical settings.[163, 180] In a large cohort of patients with AKI after coronary angiography, risk of developing ESRD increased in those with AKIN 1 by 60% and by >11-fold in those with AKIN 2+3.[181] Among a population of general hospitalized patients with AKI that required dialysis, risk of ESRD after 5 years increased >6-fold than in patients with AKI who didn't require dialysis during hospital admission.[182] Five-year incidence of ESRD was 0.3% among patients without dialysis-dependent AKI and 3.8% among patients who had dialysis during hospitalization.[182]

Several studies in different clinical settings, especially those with large cohorts of patients similar to ours, who underwent coronary angiography, show increased risk for ESRD among patients with AKI, even in its mildest form. The mechanism behind the association is not known, but could reflect an accelerating effect of AKI on decreasing kidney function as part of the ageing process or on other pathways that lead to impaired ultrafiltration, or it could be a proxy for a more vulnerable category of patients with increased risk for ESRD.

Dialysis is life-saving for patients but very physically and psychologically demanding. It is also associated with high health care costs and high annual risks of morbidity and mortality. These patients should be under close surveillance of a nephrologist who can take every necessary action to prevent or delay the progression of kidney failure.

# CONCLUSIONS

- Acute kidney injury after CABG, including small changes of serum creatinine is associated with postoperative complications and mortality within 60 days of surgery.

- Acute kidney injury after CABG is strongly correlated with long-term all-cause mortality and increased long-term risk for myocardial infarction.

- We found a weak association between AKI and stroke after CABG, but the association disappeared after taking death into account as a competing risk.

- Acute kidney injury after CABG is correlated with increased long-term risk for end-stage renal disease.

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